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THE REDUCTION OF N-BENZYL AND N-METHYL PYRAZINIUM SALTS WITH SODIUM BOROHYDRIDE AND THE NUCLEAR MAGNETIC RESONANCE PROPERTIES OF N-BENZYL PIPERAZINES

JOHN JOSEPH THOMAS

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BY

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I. INTRODUCTION

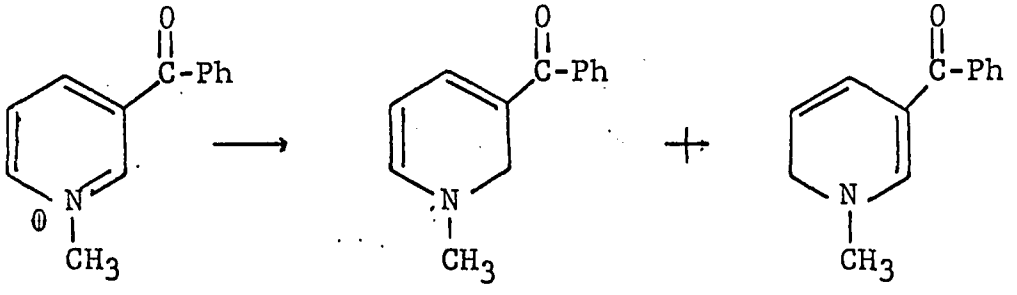
The hydride ion moiety of complex metal hydrides has long been known to undergo reaction with electrophilic sites in heterocyclic molecules. Lithium aluminum hydride, a very reactive reducing agent, is capable of reducing aromatic nitrogen heterocyclics which have carbon atoms that are more electrophilic than those of benzene.[1]

Quaternization of aromatic nitrogen heterocycles greatly increases the electrophilicity and allows the ring to be attacked by less reactive complex metal hydrides such as sodium borohydride. The mechanistic interpretation of borohydride attack on quaternary nitrogen compounds has been extrapolated from the experimental results obtained from extensive studies of pyridinium ion reductions. The pyridinium ion reductions should prove an excellent guide to reduction of pyrazinium ions because the effect of the heteroatom in both systems is similar.

The reactive sites of the pyridinium ion are the 2-,4-and 6-positions. The initial reaction of hydride occurs at the 2 or 6-positions predominantly due to the proximity of the positively charged nitrogen atom.[2,3] (See Equation 1). Initial attack at the 2-position produces a 1,2-dihydropyridine which undergoes further reduction to form a 1,2,5,6-tetrahydropyridine. Initial attack at the 6-position of a 3-substituted pyridinium ion results in the formation of a 1,6-dihydropyridine which undergoes no further reduction.[4-7] This mechanism was dramatically shown by use of the ultraviolet spectrophotometer.[2] The 475-490 mμ maximum resulting from the 1,2-dihydropyridine (II) increased rapidly in intensity and then slowly decreased, while the maximum at 388 mμ due to the 1,6- (or 1,4-)-dihydropyridine (III) maintained the same intensity over a long period of time.

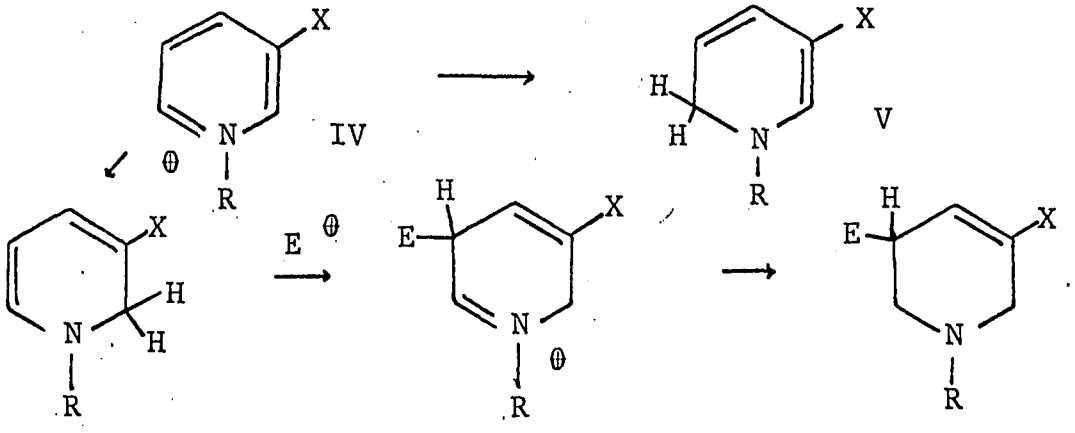
These results strongly supported the general mechanism of borohydride reduction of pyridinium salts proposed by Katritzky[8] which involved reaction of a proton with the dihydropyridine (VI) followed by reduction of the resultant immonium salt (VII) to the tetrahydropyridine (VIII). (See Equation 2).

Equation 1



I II III

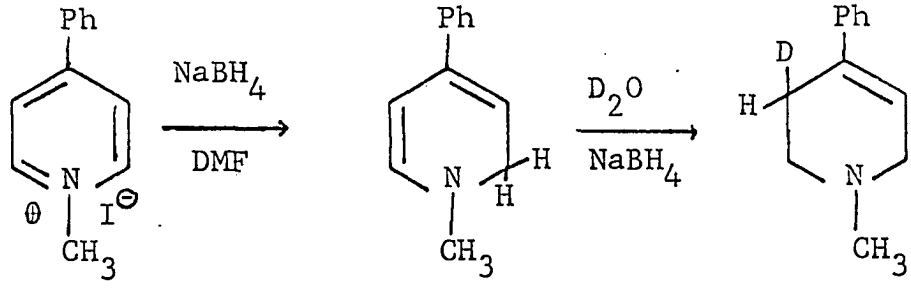
Equation 2



VI VII VIII

It was definitely shown that the electrophile is a proton and not borane and that the electrophilic attack occurs at the 3 and/or 5-position by deuterium labeling experiments on the reduction of 1-methyl-4-phenylpyridinium iodide (IX). IX was dissolved in dimethyl formamide and was treated with deuterium oxide and sodium borohydride. The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (XI) which was isolated was shown to have a deuterium atom located at the 3-position as would be expected if the electrophile in the Katritzky equation were a deuteron.[9,10] (See Equation 3).

Equation 3



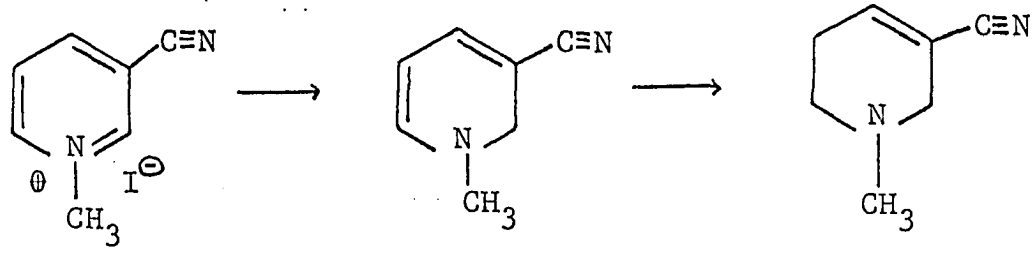
IX X XI

Sodium borohydride reduction of the enamine of cholestenone was originally proposed to occur by attack of borane on the dihydro intermediate.[11] Even precluding the above evidence, this mechanism seems unlikely for borane should prefer to react with the protonic solvent in preference to the enamine system. Borane attack also seems unlikely because the organoborane formed should be stable and isolable under the usual conditions of reaction and work-up, but the expected organo-borane has never been

isolated or observed.

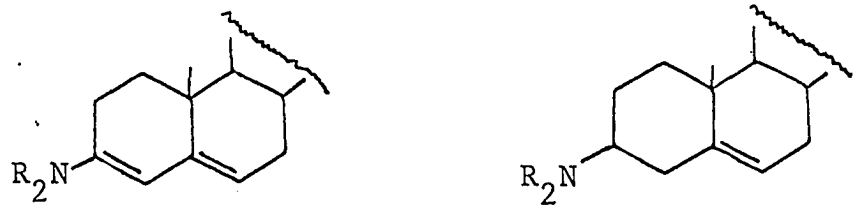
It is theoretically possible for an electrophile to attack at one of two positions in dihydropyridines; the central carbon (3-position) or terminal atom (5-position) of the dienoid system. Since 1,2,5,6-tetrahydronicotinonitrile (XIV) was obtained from the reduction of 1-methyl-3-cyanopyridinium iodide (XII)[7], and 3-dimethylamino-5-cholestene (XVI), from the reaction of the enamine of cholestenone with $NaBH_4$, attack at the 3-position was assumed.[11] (See Equations 4 and 5).[12]

Equation 4



XII XIII XIV

Equation 5

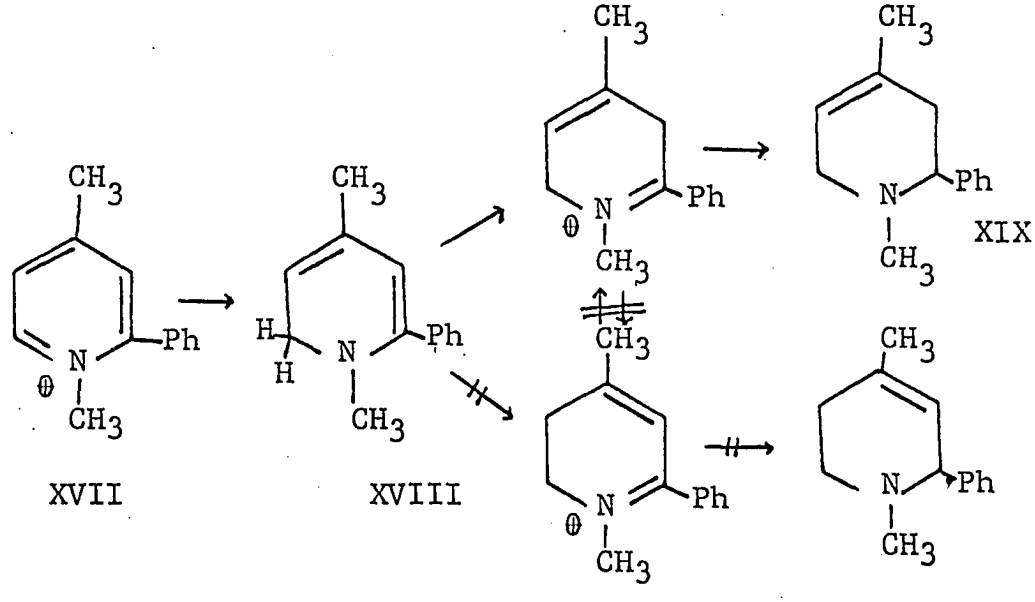


XV XVI

Additional evidence for 3-position attack was obtained by determining the double bond position in the tetrahydropyridine XIX, which was obtained from sodium borohydride reduction of 1,4-dimethyl-2-phenylpyridinium iodide (XVII).[12] Only attack at the 3-position could account for the product since equilibration of immonium isomers was precluded by the deuterium labeling experiments described previously. Attack at the 3-position of dienamines would be predicted on the basis of Ingold's rule, which states that protonation of the anion of α-β-unsaturated esters occurs at the α-position. (See Equation 6).

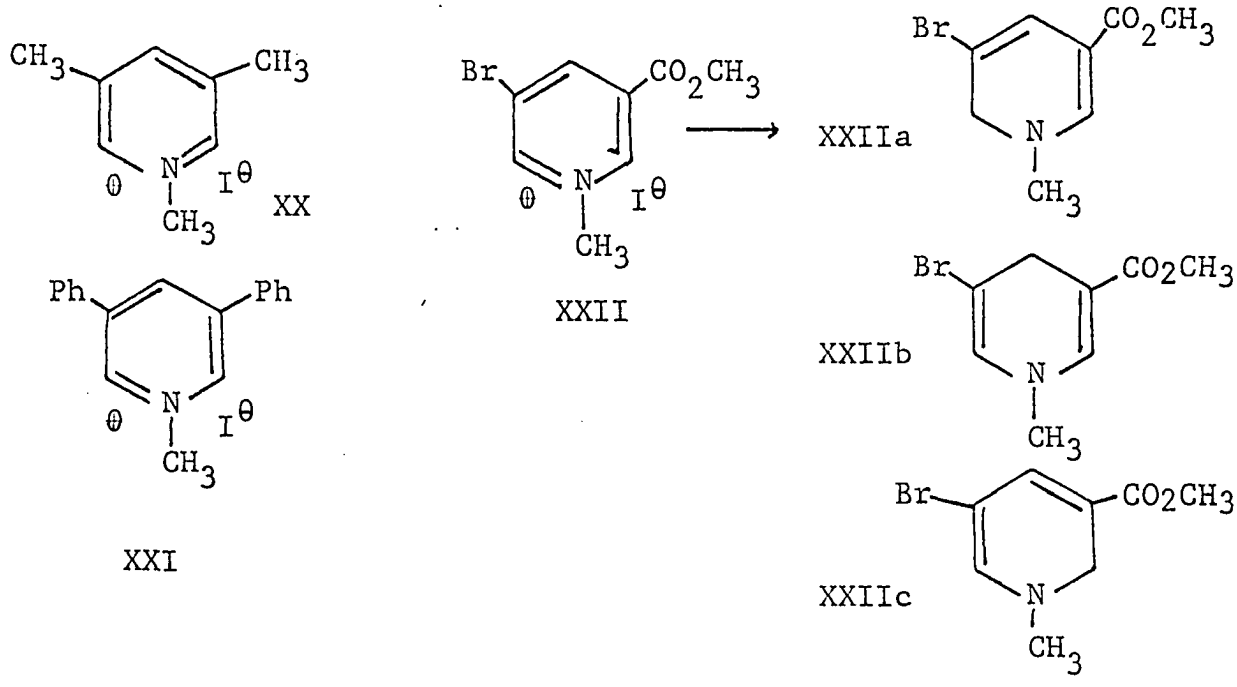
Sodium borohydride reductions of pyridinium ions are influenced by steric considerations. If there is a 2-substituent on the pyridinium salt initial attack of hydride ion will occur predominantly at the 6-position.

Equation 6



If there are substituents in the 3- and 5-positions, the rate of protonation is markedly decreased after the initial attack of hydride ion is completed. For example, the reduction of 1,3,5-trimethylpyridinium iodide (XX), 1-methyl-3,5-diphenylpyridinium iodide (XXI), and 1-methyl-3-bromo-5-methoxycarbonyl pyridinium-iodide (XXII) gave dihydropyridines which markedly resisted further reduction.[13] (See Equation 7).

Equation 7



Piperidines have been reported formed from reduction of pyridinium salts with sodium borohydride. Piperidine formation results from initial attack at the 4-position and subsequent reduction of the enamines formed. (See Equation 8). The amount of piperidine formed can be related to the steric bulk of the nitrogen substituent as shown in Table 1.[14]

Equation 8

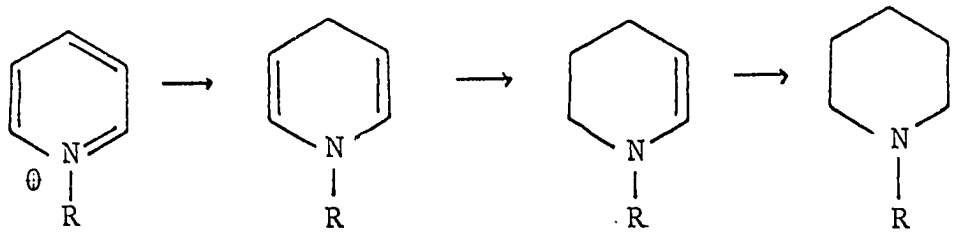


Table I

R	% Piperidine
CH_3	0
$-CH_2-CH_2-CH_3$	5
CH_2-Ph	12
$-CH(CH_3)_2$	28

In summary, the essential points of the mechanism of the sodium borohydride reduction of pyridinium salts are as follows.[15]

1. The initial point of attack by hydride is at the 2- or 6-positions of the pyridinium ring unless there is serious steric interference to reaction at these points.

2. The dihydropyridine formed will be protonated at the 3- and/or 5-position provided there is again no steric interference to reaction at these points.

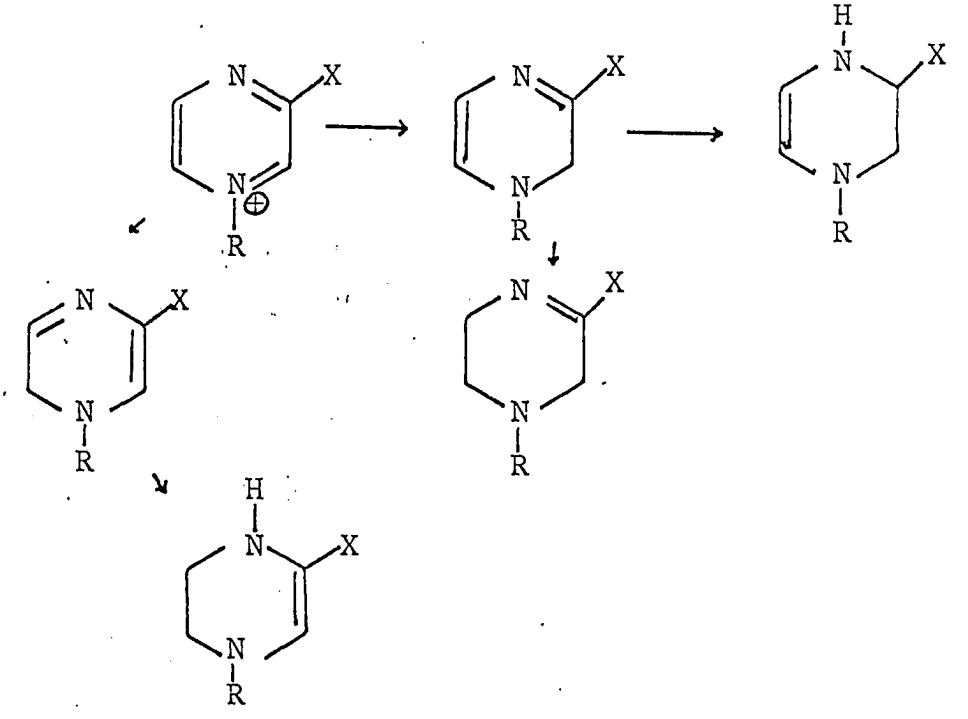
3. Hydride ion will then attack the immonium salt produced by protonation of the dihydropyridine, and thus form a tetrahydropyridine.

4. Bulky nitrogen substituents will aid the formation of piperidine by slowing the rate of hydride attack at positions 2 and 6 relative to position 4.

5. Substituents in the 3- and 5-positions will markedly decrease the rate of reduction of the dihydropyri-

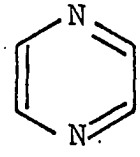
dine formed after initial reaction of hydride ion at the 2- or 6-positions.

Assuming that a similar reaction pathway would occur on reaction of sodium borohydride with a pyrazinium salt the initially formed dihydropyrazine would have several choices for further reaction. The C=N at the 3 position could undergo reduction or a proton from the solvent could undergo reaction at the 5- or 6-position. Any of these possibilities would lead to intermediates which would undergo further reduction to the piperazine. An enamine such as that in 1,2,3,4-tetrahydropyrazine usually requires acidic conditions for reduction by sodium borohydride. Thus a study of the reaction of pyrazinium salts with sodium borohydride was of interest to determine the extent of saturation of the ring in the product. It would be anticipated that the sensitivity of this reaction to steric and electronic effects would permit all pathways to occur depending upon the position and nature of substituents.



II. DISCUSSION

Pyrazine (XXIII) is a 6-membered, heterocyclic, aromatic compound containing 2 nitrogen atoms in the 1- and 4-positions. Its dipole moment is zero and the aromatic nature of the ring system was proven when the bond distances were measured in an x-ray study of the tetramethyl derivative (XXIV).[16]



XXIII

Pyrazine (XXIII) is a weak base (pKa = 0.6) as compared with pyridine (XXV) (pKa = 4.4) but still in large measure resembles pyridine (XXV) and pyridazine (XXVI) in chemical properties. Pyrazine (XXIII) either is not attacked or is decomposed by treatment with electrophilic reagents. Both pyrazine mono- and di-N-oxides (XXVII and XXVIII) have been prepared.[16]

The reduction of pyrazine to piperazines has been reported using procedures similar to those effective in the reduction of pyridines. Thus sodium and alcohol, metal and acid, and catalytic hydrogenation have been shown to be effective. The latter method is, of course, the most convenient procedure.[16a] Reduction of pyrazinium salts is less well investigated; however, by analogy to pyridine it would be anticipated that this type of reaction would occur more

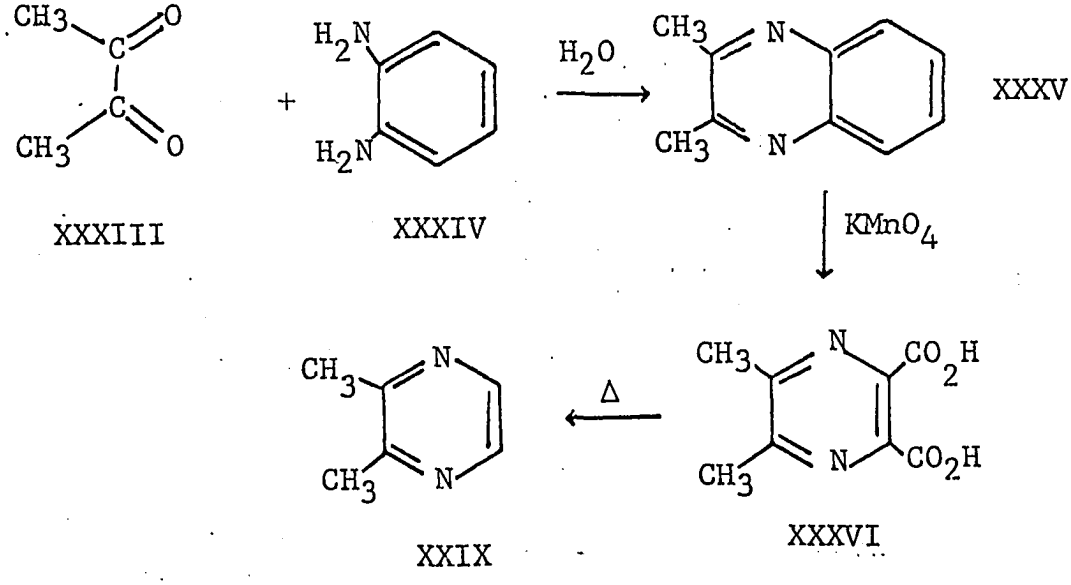
easily. To investigate this question a number of pyrazines were prepared and converted to the corresponding quaternary salts for reduction with sodium borohydride.

1. Preparation of the Pyrazines

Most of the alkyl methyl pyrazines used in the present work as well as pyrazinecarboxamide (XLIV) were available commercially.[17] 2,3-Dimethyl-(XXIX), 2,3-diphenyl-(XXX), 2,5-diphenylpyrazine (XXXI), and pyrazinonitrile (XXXII) were prepared by standard methods as described below.[17]

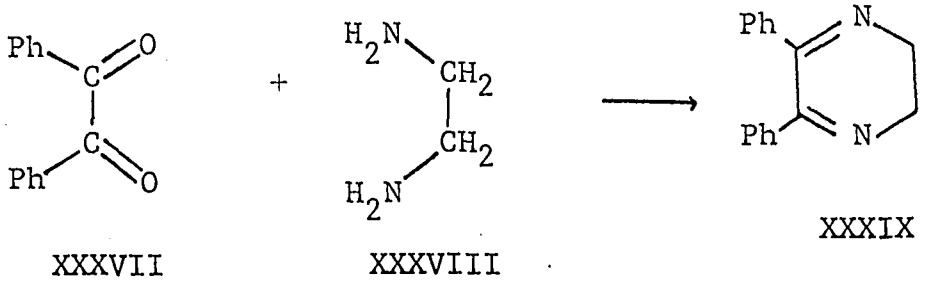
2,3-Dimethylpyrazine (XXIX) was prepared by the condensation of 2,3-butanedione (XXXIII) with o-phenylenediamine (XXXIV) to obtain XXXV. The 2,3-dimethyl quinoxaline (XXXV) was oxidized with potassium permanganate to 5,6-dimethylpyrazine-2,3-dicarboxylic acid (XXXVI) which on decarboxylation gave XXIX.[18] (See Equation 9).

Equation 9

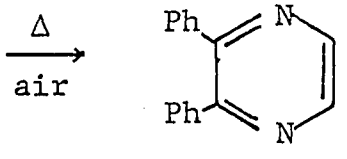


2,3-Diphenylpyrazine (XXX) was obtained by the dehydrogenation of the condensation product, 5,6-dihydro-1,2-diphenylpyrazine (XXXIX), of benzil (XXXVII) with ethylenediamine (XXXVIII).[19] (See Equation 10).

Equation 10



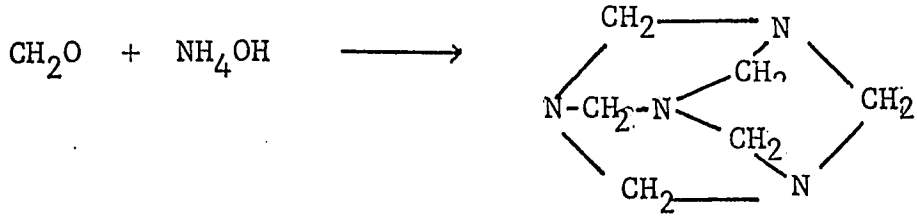
XXXVII XXXVIII XXXIX



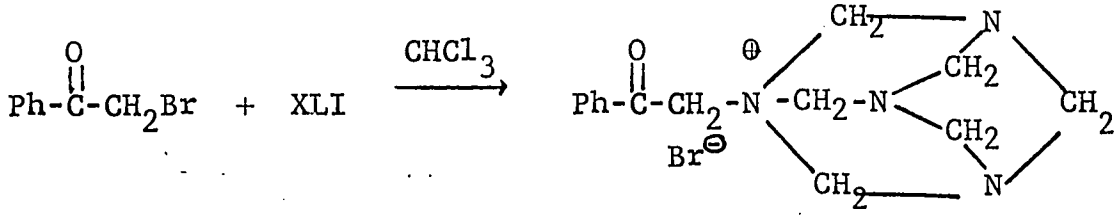
XXX

2,5-Diphenylpyrazine (XXXI) was obtained in the following manner. Phenacyl bromide (XL) was treated with hexamethylenetetramine (XLI) and the salt XLII was obtained. XLII was then hydrolyzed to the mixed salts of α-aminoacetophenone (XLIII).[20,21] These salts were heated under reflux in ethanolic ammonium hydroxide solution to obtain XXVI.[22] (See Equation 11).

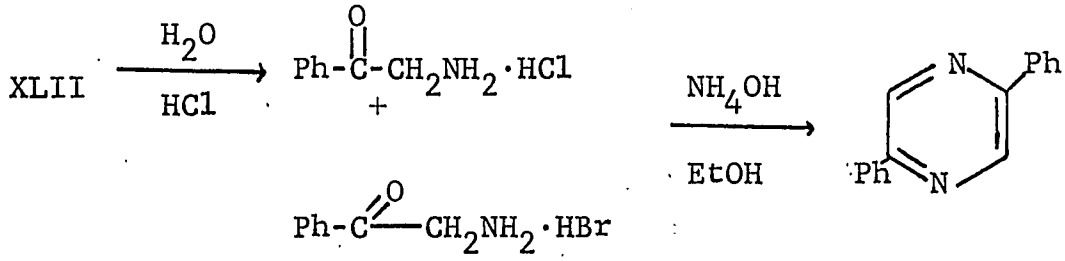
Equation 11



XLI



XLII

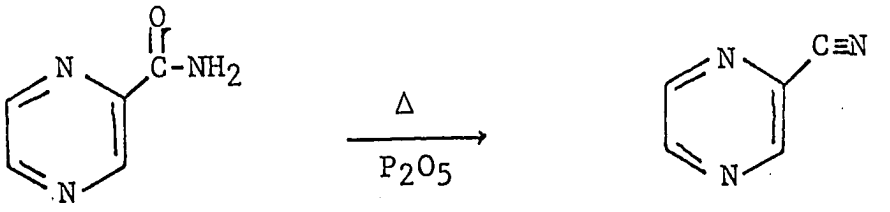


XLIII

XXXI

Pyrazinonitrile (XXXII) was prepared by dehydration of pyrazinecarboxamide (XLIV) with phosphorous pentoxide.[23] (See Equation 12).

Equation 12



XLIV XXXII

2. Quaternization of the Pyrazines

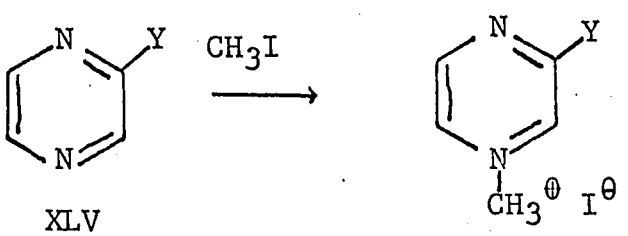
The formation of quaternary salts of pyrazines occurs by an SN_2 reaction of pyrazine with the alkylating agent. Some examples of quaternizing agents are alkyl halides, dimethyl sulfate and methyl-p-toluenesulfonate. Quaternization of one nitrogen atom in pyrazines introduces a positive charge into the aromatic system which greatly decreases the basicity and nucleophilicity of the second nitrogen atom. Thus a substantial energy barrier hinders the formation of di-quaternary salts of pyrazines. The literature abounds with examples of alkylations in which the use of a large excess of alkyl halide leads only to mono-alkylation.[24] Curphey, however, has reported that substituted pyrazines can be converted to diquaternary salts by the action of triethyloxonium fluoroborate in refluxing dichloroethane.[25]

Steric effects have been shown to be very important in directing the course of the quaternization reactions of nitrogen heterocycles. Brown and Cahn[26] studied the reactions of 2-, 3-, and 4-alkylpyridines with methyl, ethyl, and isopropyl iodides in nitrobenzene. A higher activation energy was observed for the quaternary salt formation with 2-substituted pyridines than the 3- or 4-substituted analogs. As the effective size of the 2-substituent or the alkylating agent increases there was a further increase in the activation energy. If the pyridine ring was substituted in the 3-position and the bulk of the substituent was increased, a steady increase in quaternization rates was observed. This increase in rate was rationalized as being due to an increase in the inductive effect accompanying the increase in size of the 3-alkyl substituent.

The heats of reaction were determined for the protonation of a series of 2-substituted pyridines with methanesulfonic acid in nitrobenzene. A decrease in the heats of reaction was observed as the size of the 2-substituent increased. These results of Brown would indicate that "thermodynamic effects are operative in protonation and kinetic influences are more important in quaternization.[27]" The order of heats of reaction of the proton reaction with the substituted pyridine suggests that the electronic effect of the substituent on the basicity of the pyridine is important; however, in quaternization reactions the steric effect is very strong.

Cheeseman showed, from spectroscopic evidence, that 2-amino- and 2-diethylamino-pyrazine (XLV) undergo reaction with alkyl halides at the 4-position although protonation occurs at position-1.[26,29] Other substituted pyrazines which have been converted to quaternary salts of structure (XLVI) include 2-chloro- and 2-carbamoyl compounds (XLV).[30] Quaternization at N-4 would be expected in these compounds because of the steric interference of the 2-substituent with quaternization at the 1-position.

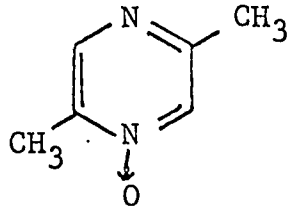
Equation 14



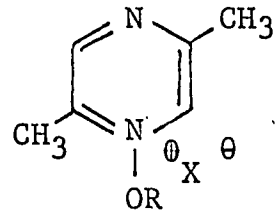
XLV XLVI

Y = NH_2, NEt_2, Cl, $CONH_2$

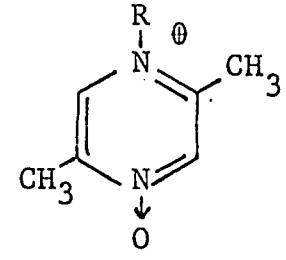
In view of the apparent difficulty in forming a quaternary salt at the nitrogen adjacent to a substituent, it is surprising that 2,5-dimethylpyrazine-1-oxide (XLVII) does not undergo reaction with methyl iodide or benzyl chloride by formation of an O-alkyl pyrazinium salt (XLVIIIa). Reaction of the oxide XLVII with these alkylating agents occurs at the 4-position to give XLVIIIb.[31]



XLVII



XLVIIIa



XLVIIIb

The results of these quaternization reactions suggested that the alkylation of the 2-substituted pyrazines used for this study would occur at the 4-position. It was further anticipated that 2,3-disubstituted and 2,3,5,6-tetrasubstituted pyrazines, where quaternary salt formation must occur adjacent to a substituent, would be resistant to reaction with an alkylating agent. These postulates were supported by experimental observations.

During the course of the present work 2,3,5,6-tetramethylpyrazine (XXIV) gave no reaction with benzyl bromide in refluxing acetone, while the less sterically hindered 2-methyl (XIX), 2,5-dimethyl (L), 2,3-dimethyl (XXIX), and 2,6-dimethyl (LI) pyrazines, and pyrazine carboxamide (XLIV), were converted to benzyl quaternary salts under these conditions. 2,3-Dimethylquinoxaline (XXXV), 2,5-diphenylpyrazine (XXXI), 2,3-diphenylpyrazine (XXX), and

2,3,5,6-tetramethylpyrazine (XXIV), were alkylated, however, with methyl iodide in dimethylformamide, methanol, and acetone respectively. Pyrazinonitrile (XXXII) was alkylated with dimethyl sulfate in benzene. A summary of these data is given in Table II.

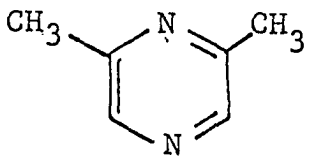
It can be seen that a problem could arise in assigning the position of alkylation with 2,6-dimethyl-pyrazine (LI), 2-methyl-pyrazine XLIX, pyrazinonitrile (XXXII), and pyrazine carboxamide (XLIV). In view of the fact that Brown, et. al.[27], found steric considerations to predominate in quaternization reactions, quaternization at the 4-position would be expected.

Additional evidence that quaternization occurred at the 4-position was obtained in the present research. The fact that 2,3,5,6-tetramethyl pyrazine (XXIV) was inert to reaction with benzyl bromide strongly suggested that reaction of 2,6-dimethylpyrazine (LI) with benzyl bromide occurred at the 4-position. In view of this fact it would seem more likely that quaternization of 2-methylpyrazine (XLIX) would also occur at the 4-position.

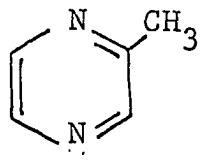
R. K. Hill has shown that the nuclear magnetic resonance spectra of cis-or trans-N-benzyl-3,4-dimethylpyrrolidines show a singlet for their benzylic hydrogens whereas cis-and trans-N-benzyl-2,6-dimethylpiperidines show a singlet and a quartet respectively.[32] Thus the presence of an equatorial methyl group substituted on the carbon adjacent to the nitrogen atom presents an environment which results in detectable non-equivalent geminal protons in the benzylic group. If the methyl substituent is moved to the 3-position the non-equivalence of the benzylic protons cannot be detected because the dissymetric environment is too far removed.

If quaternization of 2-methylpyrazine XLIX occurred at the 4-position, the product after reduction with sodium borohydride would give 1-benzyl-3-methyl piperazine (LII). The benzylic protons should show a singlet since the asymmetric environment is too distant. If, however, quaternization occurred at the 1-position, the product upon reduction would give 1-benzyl-2-methylpiperazine (LIII) whose benzylic hydrogens should exhibit a quartet in the nuclear magnetic resonance spectrum. The compound which was isolated showed only a singlet and was thus assumed to be 1-benzyl-3-methylpiperazine (LII) proving that the original quaternization took place on the 4-position.

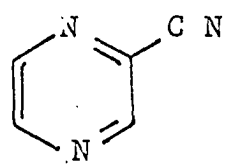
Thus this present work has shown that quaternization of pyrazines is strongly influenced by steric and electronic effects. 2- And 6-substituted pyrazines were preferentially quaternized at the 4-position. Tetra-substituted pyrazines as well as 2- and 3- or 2- and 5-phenyl substituted pyrazines, and 2-substituted quinoxalines can be quaternized readily only with small alkylating agents. Pyrazines with electron withdrawing substituents are quaternized only with great difficulty.



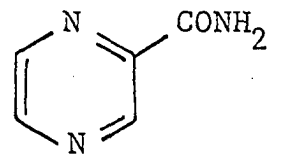
LI



XLIX



XXXII



XLIV

TABLE II

Reactions of Pyrazines with Various Alkylating Agents

Pyrazine	Quaternizing Agent	Solvent	Temp.	Yield of pyrazinium Salt
2,3,5,6-Tetramethyl (XXIV)	Benzylbromide	acetone	reflux	none
2,3,5,6-Tetramethyl (XXIV)	Methyliodide	acetone	reflux	35% (LIV)
2,6-dimethyl (LI)	Benzylbromide	acetone	reflux	88% (LV)
2,5-dimethyl (L)	Benzylbromide	acetone	reflux	63% (LVI)
2,3-dimethyl (XXIX)	Benzylbromide	acetone	reflux	50% (LVII)
2-methyl (XLIX)	Benzylbromide	acetone	reflux	50% (LVIII)
2,5-diphenyl (XXXI)	Benzylbromide	acetone	reflux	None
2,5-diphenyl (XXXI)	Methyliodide	D.M.F.	reflux	65% (LIX)
2,3-diphenyl (XXX)	Methyliodide	Methanol	reflux	27% (LX)
Pyrazine carboxamide (XLIV)	Benzylbromide	Methanol	reflux	8.2% (LXI)

Pyrazinonitrile (XXXII)	Dimethylsulfate	Benzene	R.T.	18% (LXII)
Pyrazinonitrile (XXXII)	Benzylbromide	Acetone	reflux	none
Pyrazinonitrile (XXXII)	Benzylbromide	Butanol	reflux	none
Pyrazinonitrile (XXXII)	Benzylbromide	Nitrobenzene	reflux	none
Pyrazinonitrile (XXXII)	Methyliodide	Acetone	R.T.	Trace
2,3-Dimethyl-quinoxaline (XXXV)	Benzylbromide	Acetone	reflux	none

3. Reduction of Pyrazinium Salts with Sodium Borohydride

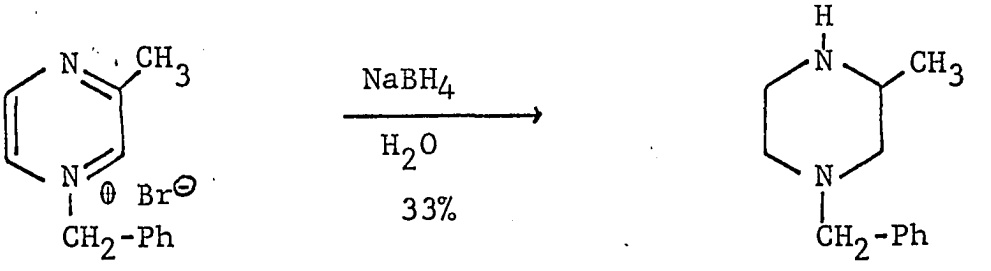
The reaction of sodium borohydride with substituted pyridinium salts has been shown to yield di- and tetrahydropyridines as the major products. The dieneamine system formed by the initial attack of the hydride on the pyridinium ion undergoes reaction with a proton from the solvent to give an immonium salt. This function is reduced further by sodium borohydride to give a tetrahydropyridine.

The objective of this present work was to study the reaction of sodium borohydride with pyrazinium salts. A pyrazinium salt could form only enamine or imine double bonds by hydride ion reaction, and thus it was anticipated that sodium borohydride reduction of pyrazinium salts in protic solvents would form piperazines and not partially reduced pyrazines. Since no example of the reduction of pyrazinium salts with sodium borohydride had been reported, this hypothesis could not be checked in the literature. The benzo derivative, 1-methyl- and 1-ethylquinoxalinium salts, have been reported to form 1-substituted 1,2,3,4-tetrahydroquinoxalines.[33]

The 1-benzylmethyl pyrazinium salts obtained in the present work were converted by sodium borohydride in water solution to the 1-benzylmethylpiperazines in varying yields. The products were identified by analysis as well as by analysis of their phenylthiourea derivatives. The infra-red spectrum showed an N-H, band at 3300 $cm.^{-1}$, phenyl-H, at 700, and no absorption between 1600 and 1800 $cm.^{-1}$. The ultraviolet spectrum showed only phenyl absorption. The nuclear magnetic resonance showed phenyl-H absorption at $\sim$ 7.3 p.p.m., benzylic absorption at $\sim$ 3.4 p.p.m., N-H at $\sim$ 1.35 p.p.m. and

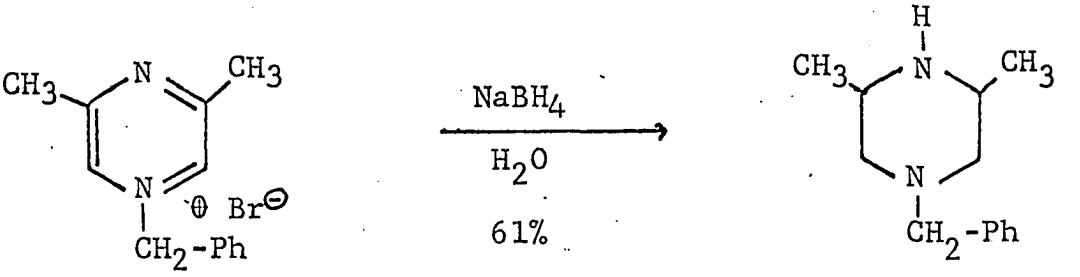
CH_3 at ~ 0.9 p.p.m. (See Equations 16, 17, 18, and 19 and Table III).

Equation 16



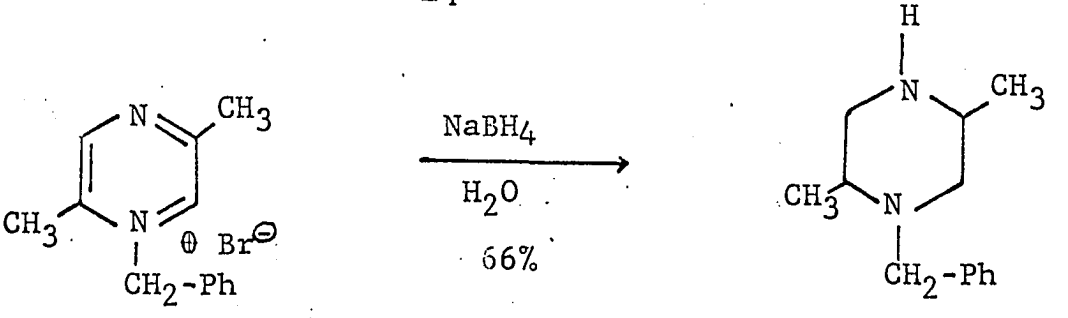
LVIII LXIII

Equation 17



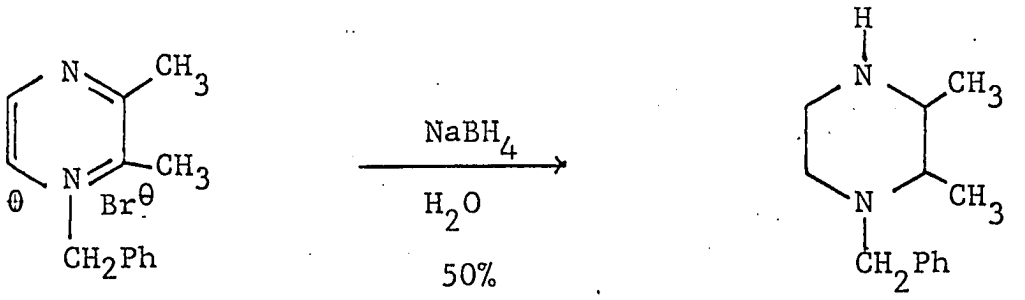
LV LXIV

Equation 18



LVI LXV

Equation 19



LVII LXVI

Of the several 1-benzylmethylpiperazines prepared in this study only cis-1-benzyl-3,5-dimethylpiperazine (LXIV) and 1-benzyl-3-methylpiperazine (LXIII) have been reported previously. The refractive index of LXIV (n^{20} = 1.5271) from the sodium borohydride reduction did not correspond with the value (n^{20} = 1.5363) reported in the literature, however. The refractive index of LXIII corresponded exactly with that reported in the literature (n^{25} = 1.5337).[35] The melting point of the picrate of LXIV, 245-246° corresponded with that reported, 245-247°.[34]

All the other pyrazinium salts gave tarry products upon reduction with sodium borohydride. The intermediates which would form during the reduction of the pyrazinium salts (dihydro- and tetrahydro-pyrazines) are known to be unstable, unlike the intermediates produced in the reduction of the pyridinium salts. It might be expected that electron withdrawing substituents such as phenyl, carboxamido, and cyano would stabilize the partially reduced pyrazine toward reaction with hydride ion. Thus the rate of reactions forming piperazines would be decreased. This decrease in rate of piperazine formation would allow the side reactions of hydrolysis and polymerization to become the predominant and give intractable oils as products.

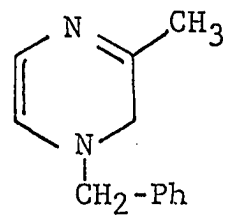
The reduction of pentamethylpyrazinium iodide (LXIV) also gave an intractable product. The steric bulk of the methyl groups probably protected the ring positions from reaction with borohydride and therefore prevented piperazine formation. Thus hydrolysis and polymerization occurred instead.

The course of the reduction of all the pyrazinium salts was followed by observing the changes in absorption in the ultraviolet and visible spectra. The reactions were run in the cells of a recording spectrophotometer. Water solutions of the 1-benzylmethyl pyrazinium salts underwent reduction too rapidly in the ultraviolet spectrograph cell; thus more information was obtained when other solvents such as dimethyl formamide and 2-propanol were used. The absorption maxima of the salts and the intermediates found in various solvents in the reduction process are listed in Table IV. The more important spectra will be discussed in this section.

The spectrum of 1-benzyl-3-methylpyrazinium bromide (LVII) (λ_{max} = 278 mμ, log ϵ = 3.62, 2-propanol) on reduction with sodium borohydride in the ultraviolet spectrophotometer cell immediately exhibited an absorption maximum at 336 mμ and a simultaneous disappearance of the 278 mμ band. The maximum at 336 mμ decreased in intensity to zero absorption.

The chromophore responsible for the maximum at 336 mμ absorption was probably (LXVII), for the corresponding dihydropyridine (LXVIII) absorbs at 330 mμ.[13] The introduction of a nitrogen atom in place of a carbon atom does not affect the ultraviolet absorption significantly and thus the two values are comparable. This is substantiated by the

fact that the reduction carried out in dimethylformamide in the ultraviolet cell shows a shoulder in the 340 mu region.



LXVII

The treatment of 1-benzyl-3,5-dimethylpyrazinium bromide (LV) (λ_{max} = 286 mμ; log ϵ = 3.84, 2-propanol) with sodium borohydride in the absorption cell caused the disappearance of the original absorption and appearance of a new maximum at 339 mμ. This band slowly decreased in intensity, shifted slightly in the bathochromic direction to 342 mu, and finally to zero absorption. The chromophore responsible for absorption in the 340 mμ region is probably due to 1-benzyl-3,5-dimethyl-1,2-dihydropyrazine (LXIX) analogous to the previous case. (See Fig. 5). A shoulder appeared again in the 340 mμ region when the reduction was carried out in the cell in dimethylformamide.

The treatment of 1-benzyl-2,5-dimethylpyrazinium bromide (LVI) (λ_{max} = 289 mμ; log ϵ = 3.91, 2-propanol) with sodium borohydride in the absorption cell again caused the appearance of a new maximum at 320 mμ which shifted hypsochromically to 300 mμ while decreasing in intensity. This phenomenum is probably due to overlapping of two chromophoric absorptions. One probably belongs to the pyrazinium salt and the other to 1-benzyl-2,5-dimethyl-1,6-dihydropyrazine (LXX). The probability of the 1,6-dihydropyrazine

formation was again verified by the appearance of a shoulder of 330 mμ region when the reduction was carried out in dimethylformamide.

These results were in agreement with those of Anderson who observed, during the reduction of methylpyridinium compounds with sodium borohydride in the ultraviolet cell, that a maximum formed at about 330 mμ in methanol and in dimethyl formamide.[13] These absorptions were attributed to the 1,2-dihydropyridine which would be formed on addition of hydride ion to the 2-position.

A water solution of pentamethyl pyrazinium iodide (LIV) (λ_{max} 305 mμ, log ϵ = 4.14, H_2O) on treatment with sodium borohydride in the ultraviolet cell, showed a slower decrease in intensity of the salt absorption band than was observed in the water solutions of the 1-benzylmethylpyrazinium salts. A bathochromic shift of the absorption maximum to 315 mμ was also observed. This bathochromic shift was probably caused by the overlapping of two chromophores which can be assigned to the pyrazinium salt (LIV) and the dihydropyrazine formed by attack of borohydride. The steric bulk of the four methyl groups probably slows the reduction process and explains the inability to obtain a piperazine product in this case.

An alcoholic solution of 1-methyl-2,5-diphenyl pyrazinium iodide (LIX) (λ_{max} 271 mμ, log ϵ = 4.33, λ_{max} 356 mμ, log ϵ = 4.31), on treatment with sodium borohydride in the cell, showed the following changes in spectrum with time.

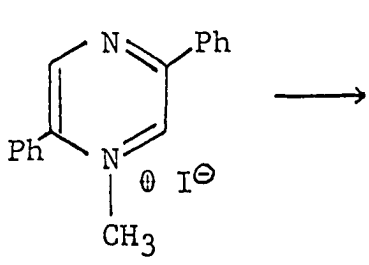
1. The bands at 271 mμ and 356 mμ, due to the parent salt disappeared almost immediately after adding sodium borohydride.

2. A band at 388 mμ began to appear and increase in intensity. The intensity of this band did not decrease in addition of more sodium borohydride. A drop of acetic acid was added and the intensity of the maximum at 388 mμ decreased dramatically to a point. No further decrease in intensity occurred on addition of more acetic acid.

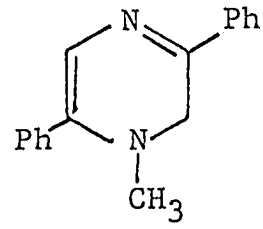
3. A band at 296 mμ appeared at about the same rate as the 388 mμ band and did not decrease in intensity on standing or on addition of more sodium borohydride. The addition of a drop of acetic acid caused the appearance of a new band at 303 mμ which decreased in intensity and shifted hyposochromically with time. (See Fig. 6).

The spectral changes were difficult to interpret because exact analogies for all the possible chromophores were not available. A few conclusions can be made, however.

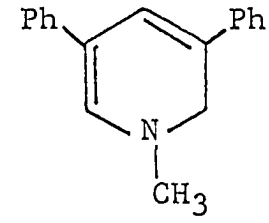
The initial attack of sodium borohydride must have been at the 6-position to form the intermediate 2,5-diphenyl-1-methyl-1,6-dihydropyrazine (LXXI) as shown. The absorption at 388 mu could best be accounted for by this structure. The closest analogy, LXXII, absorbs at 410 mμ. Complexing of Lewis acids with the 4-nitrogen of the dihydropyrazine probably prevented the adjacent phenyl ring from becoming coplanar with the dienamine system. This would explain the absorption maximum being at shorter wavelength with LXXI as compared with the dihydropyridine LXXII. Assuming the structure LXXI to be correct, the solvent would be expected to provide a proton for reaction at the 3-position with subsequent reduction to LXXIII.



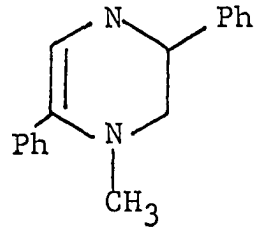
LIX



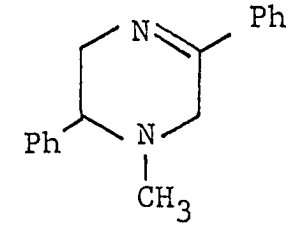
LXXI



LXXII



LXXIV



LXXIII

The styrene like chromophore of LXXIII would be expected to cause absorption at 282 mμ (log ε =2.65) which is considerably different from the absorption of the reduction reaction (λ_{max} = 296 mμ , log ε =3.83). If one assumes that the free pair of electrons of an amino nitrogen approximates the effect of a double bond in estimating ultraviolet absorption, then LXXIV would be anticipated to show a spectrum such as 1-phenyl butadiene (λ_{max} = 280 mμ ; log ε = 4.44).[37] On the basis of the large extinction LXXIV is clearly favored over structure LXXIII.

The reduction of 2,3-diphenyl-1-methyl pyrazinium iodide (LX) (λ_{max} =257mμ, log ε = 4.05; λ_{max} 343mμ, log ε = 3.79) with

sodium borohydride was accompanied by the following changes in absorption spectrum.

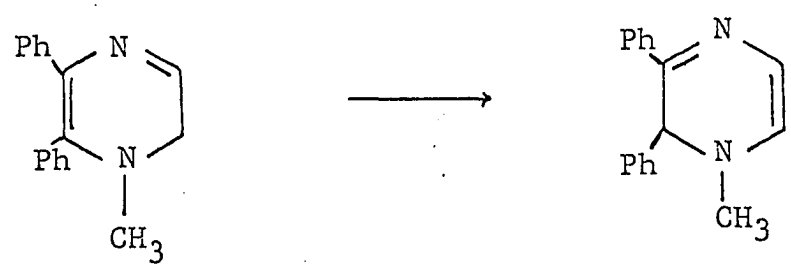
1. On addition of sodium borohydride a band at 372 mμ appeared while the band at 343 mμ seemed to disappear immediately. This new maximum in the visible region shifted bathochromically until a maximum of 405 mμ was obtained. On addition of more sodium borohydride this maximum increased in intensity and shifted to longer wavelength to give a maximum at 410 mμ.

2. Upon addition of 2 drops of acetic acid this maximum decreased in intensity to a minimum point and did not decrease further. In the ultraviolet region a band appeared at 332 mμ and shifted gradually in a bathochromic direction. A shoulder also appeared at 290-300 mμ upon addition of the sodium borohydride. Upon addition of 2 drops of acetic acid all the absorption above 235 mμ was eliminated except the decreased absorption at 410 mμ. (See Fig. 7).

The interpretation of these phenomena is exceedingly difficult, but the simplest explanation would seem to be that after the initial stage of reduction a rearrangement occurred; as shown in Equation 20.

This rearrangement may be thermodynamically favored in order to relieve the strain in the cis-stilbene system (Ph-C=C-Ph) in structure (LXXV).

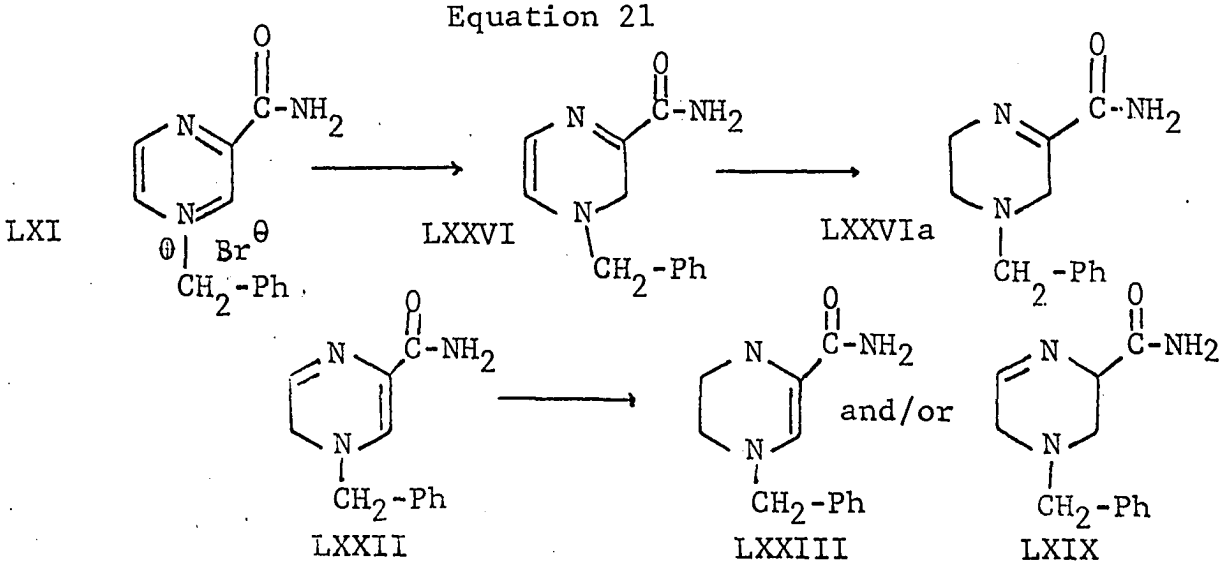
Equation 20



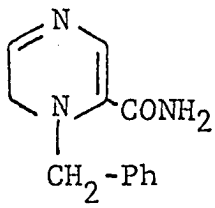
LXXV

By far the most interesting and important of the ultraviolet spectra taken was that of the reduction of 1-benzyl-3-carboxamido-pyrazinium bromide (LXI) (λ max=265 mμ, log ϵ = 4.17: λ_{max} = 308mμ, log ϵ = 3.88). On addition of sodium borohydride to a solution of LXI in water, the maximum at 308 mμ increased dramatically while the maximum at 265 mμ disappeared. The maximum at 308 mμ failed to decrease with time and did not decrease with addition of dilute acid. The initial addition of sodium borohydride to LXI caused the transient appearance of a maximum at 414 mμ in the visible region of the spectrum and decreased rapidly soon after it appeared. (See Fig. 8). These results would seem to be analogous to the reduction of 3-substituted pyridinium salts discussed in the Introduction. Apparently the initial reaction with sodium borohydride occurred at the 2-position with the formation of a tetrahydropyrazine LXXVI which underwent further reduction, but reaction at the 6-position formed a dihydro pyrazine LXXVII which was resistant to further reduction. (See Equation 21). These results were analogous to those observed by Nelson with the borohydride reduction of 1-methyl-3-carbamoylpyridinium ion.[2]

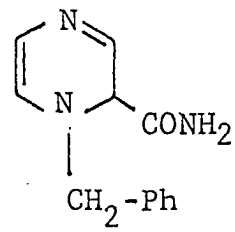
Equation 21



The changes in the ultra-violet spectrum also proved that quaternization of XLIV took place at the 4-position. The systems that would be produced, (LXXX) and (LXXXI), on reduction if XLIV had undergone salt formation at the 2-position clearly could not show the long wavelength absorption at 414 mμ.



LXXX



LXXXI

The ultra-violet absorption spectrum of 3-cyano-1-methylpyrazinium methanosulfate (LXII) (λ_{max} = 310 mμ, log ϵ = 3.80; λ_{max} = 248mμ, log ϵ = 4.24: H_2O) on addition of sodium borohydride in the cell, showed an immediate disappearance of the band at 310 mμ along with a slower disappearance of the band at 248 mμ. An absorption band at 350 mμ appeared with a shoulder of 430 mμ along with another band at 283 mμ. The 350 mμ band slowly diminished while the absorption at 283 increased to a maximum intensity which did not decrease upon addition of more sodium borohydride. On addition of one drop of acetic acid, the band at 283 mμ slowly decreased. These results are again analogous to those observed in the corresponding pyridinium ions.[13] (See Fig. 9). The changes in the n.m.r. spectrum of a deuterium oxide solution of LXII on reduction with sodium borohydride were also observed. The reduction of LXII was also examined in the nuclear magnetic resonance spectrometer tube. A deuterium oxide solution of LXII was prepared. The spectrum

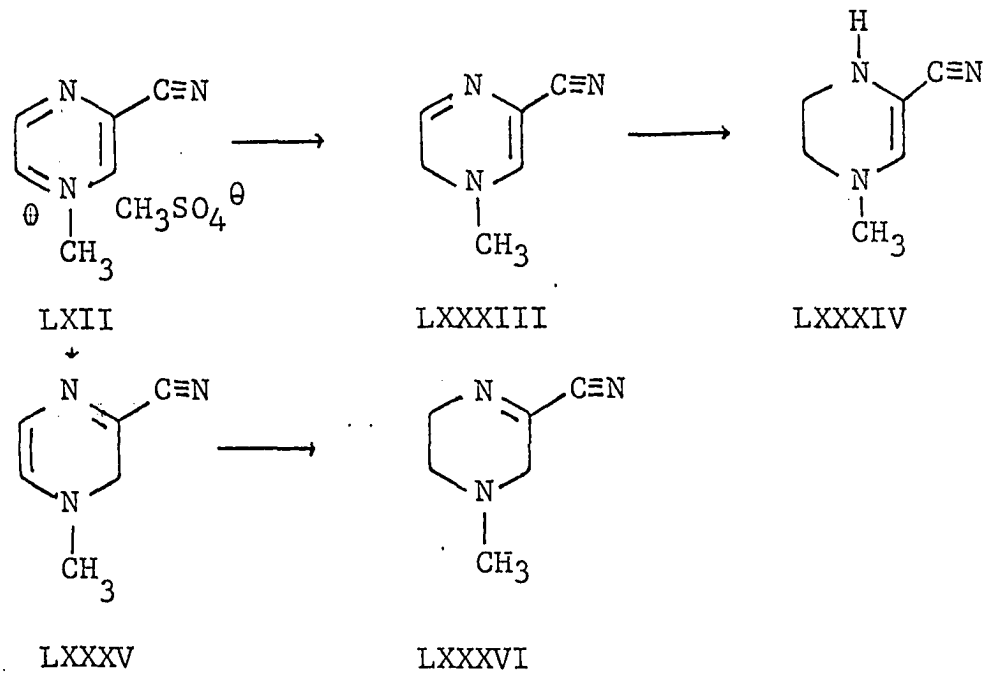
of the salt exhibited resonance bands at 3.70, 4.60, 9.37, and 9.67 p.p.m., which were assigned as $CH_3SO_4^{\ominus}$, $N \underline{\oplus} CH_3$, and ring protons respectively.[38] On addition of sodium borohydride peaks appeared at 2.90, 3.20, and 6.92 p.p.m. On addition of more sodium borohydride, the absorption at 6.92 p.p.m. decreased in intensity while peaks appeared at 0.55 and 1.88 p.p.m. which constantly increased in intensity. The absorptions at 9.37 and 9.67 p.p.m. disappeared. On addition of trifluoroacetic acid the bands at 0.55 and 1.88 p.p.m. disappeared. The resonance bands at 0.55 and 1.88 p.p.m. also appeared in a deuterium oxide solution of sodium borohydride.

The spectral changes suggest that the reduction process occurs primarily by an initial reaction of hydride at the 6-position to give LXXXIII. This is shown by the appearance of the absorption band at 350 mμ. LXXXIII contains an imine double bond which is susceptible to reaction with sodium borohydride, and reduction gives the tetrahydro pyrazine LXXXIV, which causes the absorption at 283 mμ. The absorption at 430 mμ probably indicates a small initial reaction of borohydride ion at the 2-position to form LXXXV, which is converted to LXXXVI.

The nuclear magnetic resonance data must be considered less reliable because of the possibility of precipitation of key intermediates from the concentrated deuterium oxide solution. The appearance of signals 2.90, 3.20, and 6.92 p.p.m., may be assigned to N-methyl, allylic, and vinylic hydrogens. The appearance of a sharp singlet in the vinylic region would favor assignment of structure (LXXXV) as the initial product of borohydride attack. The ultraviolet spectrum indicates, however, that this structure is formed in only minor amounts. It is possible that compound (LXXXIII)

precipitated as it was formed and thus failed to give a signal in the nuclear magnetic resonance spectrum. (See Equation 22).

Equation 22



LXII LXXXIII LXXXIV

LXXXV LXXXVI

The results of the sodium borohydride reactions with pyrazinium salts seem to follow the pathways predicted from a consideration of the corresponding reactions with pyridinium ions. Thus initial reaction of the hydride ion occurs at the position of lowest electron density, the atom adjacent to the positive charge. The further reactions of the intermediate dihydropyrazine are confused by the presence of the second heterocyclic nitrogen, but appear to follow a course predictable from a consideration of the reactions of the analagous pyridines.

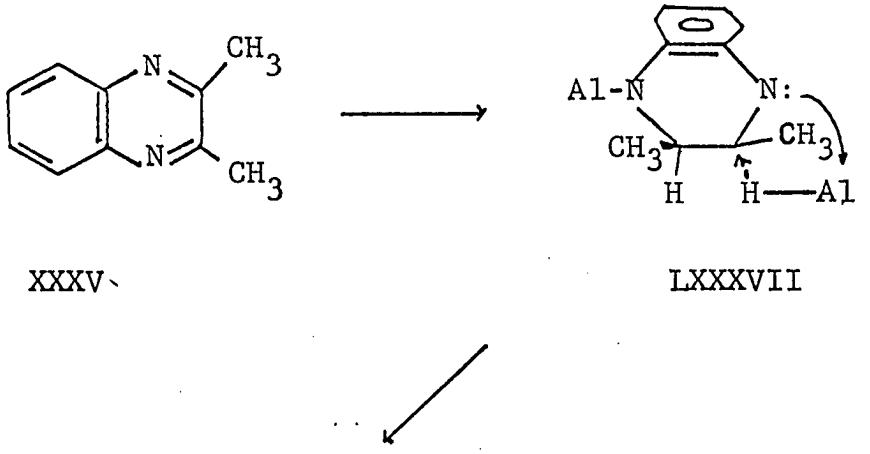
4. Stereospecificity of the Reduction with Sodium Borohydride

The reaction of hydride ion, from a metal hydride, with an unsaturated heterocyclic ring, is an irreversible reaction. Thus if isomeric forms of the product are possible, the isomer ratio reflects the relative rates of the reactions to form the isomers and the stereochemistry of the reaction is said to be kinetically controlled.[42] Since the hydride ion reductions are stepwise, the products of kinetic control may be different in stereochemistry from the products of kinetic control in catalytic hydrogenation which are usually of the cis-configuration. Under some conditions catalytic hydrogenations may be reversible and the stereochemistry of the product is then determined by the relative stabilities of the isomers under the reaction conditions, called thermodynamically controlled reactions. An understanding of the type of process involved allows the stereochemistry of the product to be used to investigate the reaction pathways of the metal hydride reductions.

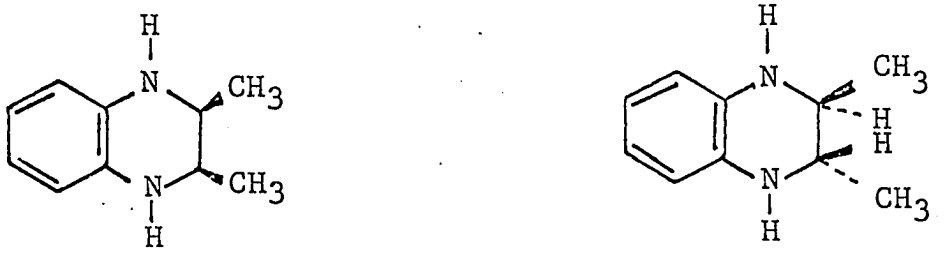
Bohlmann reported that treatment of 2,3-dimethylquinoxaline (XXXV) with lithium aluminum hydride gave a good yield of what he thought was the trans-tetrahydroquinoxaline (LXXXIX). The reaction was reinvestigated by Deselms and Mosher who obtained only the cis-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline (LXXXVIII). The fact that the cis isomer was not rearranged to the trans isomer under the reaction conditions indicated that the reaction was stereospecific.[39] The stereospecificity of this reduction may be considered to be a consequence of a two step reduction mechanism. After initial reduction of one carbon-nitrogen double bond, the second hydride ion probably is transferred

directly from the aluminohydride complex to the less hindered side of the ring system.[40] (See Equation 23)

Equation 23



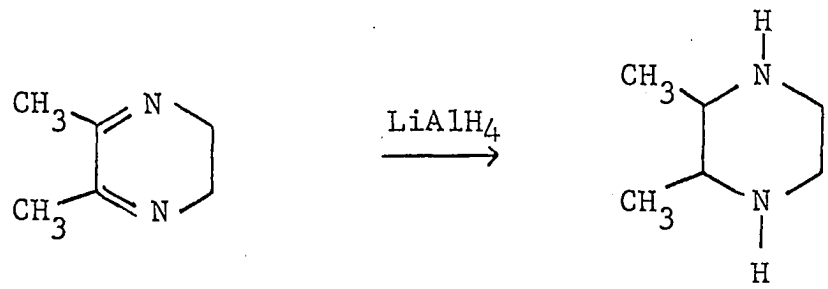
XXXV LXXXVII



LXXXVIII LXXXIX

Ishiguro and Matsumura also reported that 2,3-dimethyl-5,6-dihydropyrazine (XC) upon reduction with lithium aluminum hydride gives only the cis-2,3-dimethyl-piperazine (XCI). The stereochemical course of this reaction is probably governed by the same factor as shown in the reduction of XXXV. (See Equation 24).[41]

Equation 24



XC XCI

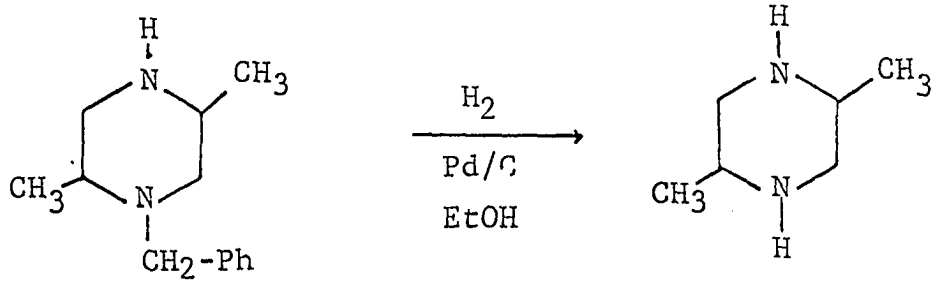
It was discovered during the course of the present work that the sodium borohydride reductions of the 1-benzyldimethylpyrazinium salts were also stereospecific reactions. The products from the reduction of the corresponding pyrazinium salts were trans-1-benzyl-2,5-dimethylpiperazine (LXV), cis-1-benzyl-3,5-dimethylpiperazine (LXIV) and cis-1-benzyl-2,3-dimethylpiperazine (LXVI). Gas liquid chromatography, as well as sharp melting points of the phenylthiourea and picrate derivatives, indicated the formation of only one geometrical isomer in each case. There was no evidence for the formation of the opposite configurational isomers of these compounds. Several gas liquid chromatographic analyses using several columns with varying temperatures and pressures, were run on these compounds and only impurities amounting to 10% or less were observed. (See Tables V and VI).

Gas liquid chromatography showed that these impurities resulted from impurities in the starting pyrazines. Thus the trans-1-benzyl-2,5-dimethylpiperazine (LXV) contained cis-1-benzyl-3,5-dimethylpiperazine (LXIV) as an impurity amounting to 10%. cis-1-Benzyl-2,3-dimethylpiperazine (LXVI) contained 1-benzyl-3-methylpiperazine (LXIII) as an impurity. These impurities were isolated by preparative gas liquid chromato-

graphy and identified by means of gas liquid chromatography, picrate melting point, nuclear magnetic resonance spectroscopy, and infra-red spectroscopy. No impurity was found in the cis-1-benzyl-3,5-dimethylpiperazine (LXIII).

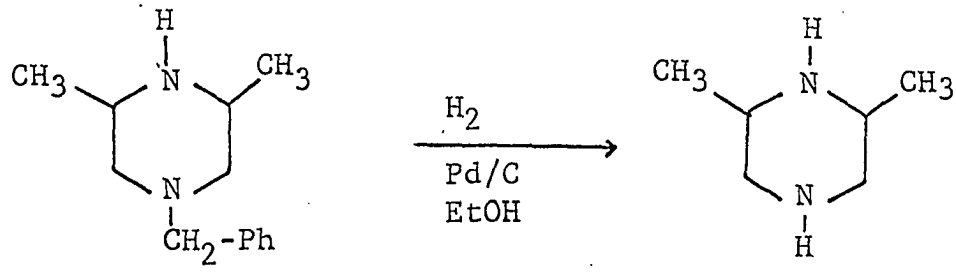
The stereochemical configuration of the 1-benzyl-dimethylpiperazine was confirmed in each case by conversion to a compound whose stereochemical assignment had been established. The 1-benzyl substituent was removed by hydrogenation and the properties of the dimethylpiperazine were compared with those reported. (See Equation 25, 26, and 27).

Equation 25



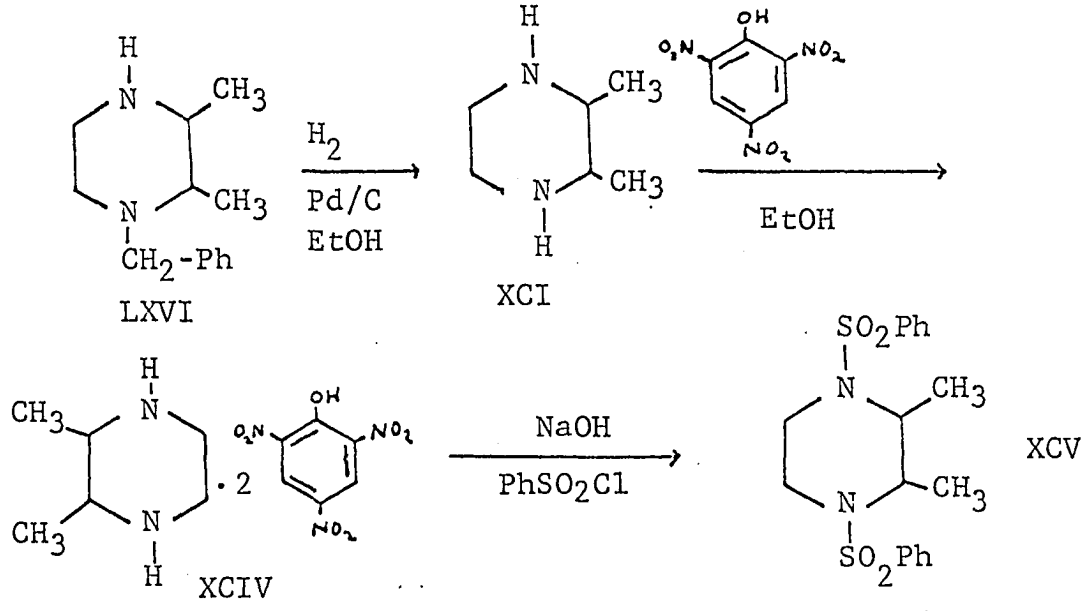
LXV — trans — XCII

Equation 26



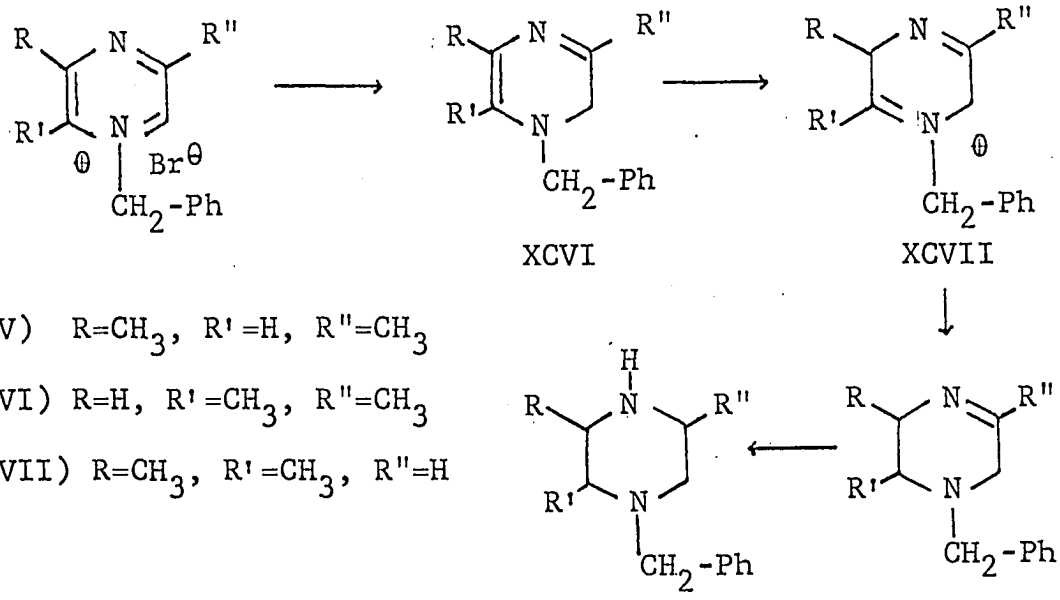
LXIV — cis — XCIII

Equation 27



The mechanism proposed by Lyle and Thomas[42] to rationalize the formation of these products from the sodium borohydride reduction assumed that the reaction with hydride was an irreversible step, and thus the stereochemistry of the products was the result of kinetic control of the reaction. The protonation step probably can be considered to be irreversible since the reaction of the ammonium salt with borohydride would be expected to be a very fast reaction. The reduction is proposed to take place in the following steps as shown in Equation 28.

Equation 28



XCVI XCVII

XCIX XCVIII

(LV) R=CH_3, R'=H, R"=CH_3

(LVI) R=H, R'=CH_3, R"=CH_3

(LVII) R=CH_3, R'=CH_3, R"=H

(LXIV) R=CH_3, R'=H, R"=CH_3

(LXV) R=H, R'=CH_3, R"=CH_3

(LXVI) R=CH_3, R'=CH_3, R"=H

The stereochemistry of 1-benzyl-3,5-dimethylpiperazine (LXIV) and 1-benzyl-2,5-dimethylpiperazine (LXV) is probably established in the last step of the reduction. Thus the mode of reaction of borohydride with a C=N determines the isomeric product formed. If the methyl group (R or R') in structure XCVIII assumes an equatorial conformation, then the pseudo-chair form can be postulated. See Fig. 1.

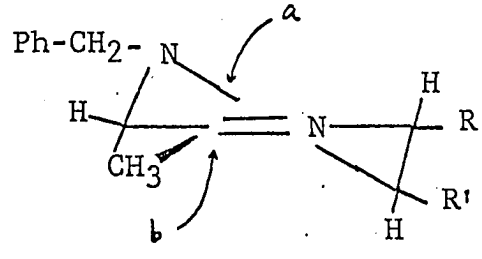


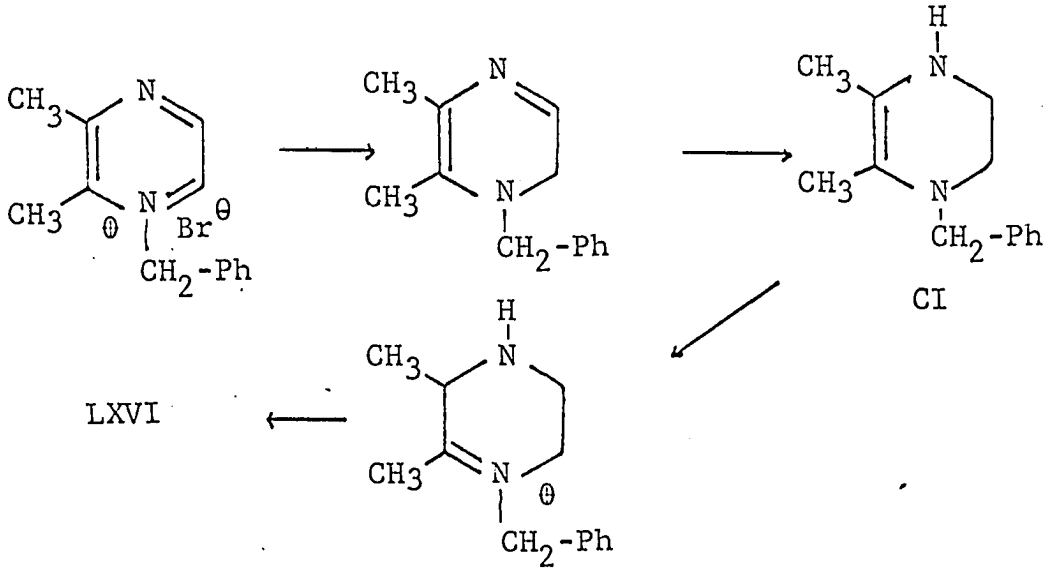
Fig. 1

If the preferred conformation is as represented by Fig. 1 then attack along route "a" would proceed via an energetically favored "chair-like" transition state and thus result in cis-1-benzyl-3,5-dimethyl piperazine (LXIV) and trans-1-benzyl-2,5-dimethyl piperazine (LXV). Reaction along path "b" would require an unfavorable "boat-like" transition state.[36]

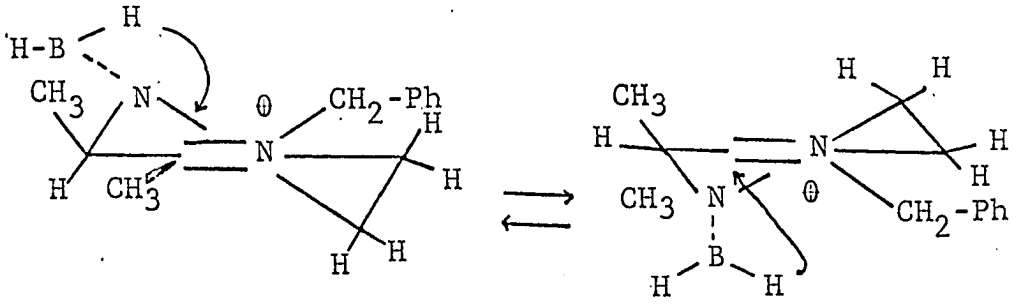
The formation of the cis isomer of 1-benzyl-2,3-dimethylpiperazine (LXVI) is more difficult to rationalize on this basis; however, the formation of this isomer from the lithium aluminum hydride reduction of the 2,3-dimethyl-quinoxaline (XXXV) and 2,3-dimethyl-5,6-dihydropyrazine (XCI) would cause it to be the expected product. The close proximity of the methyl substituent to the site of borohydride attack, probably causes the steric factors relating to the approach of the reagent to be of more importance than the small difference in energy of the two possible one-half chair conformations.

The favorable entropy factor of the intramolecular transfer of hydride from the less hindered side as postulated for the lithium aluminum hydride reduction also can be used to rationalize the formation of the cis-isomer as shown in CIII and CIV if the reduction sequence should be as shown in Equation 29. If we accept that the two conformations are in equilibrium and the reaction with borohydride is faster with CIV than with CIII, then CIV reacts as indicated to give a chair transition state which would yield the cis-product.

Equation 29



LXVI CII CI



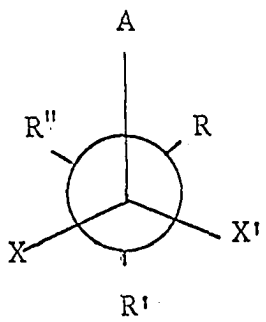
CIII CIV

5. Geminal Non-Equivalence

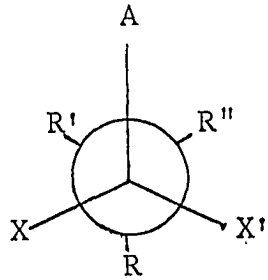
Two protons on the same carbon, which give rise to two different chemical shifts in the nuclear magnetic resonance spectrum, are said to be non-equivalent geminal protons. Geminal non-equivalence in cyclic systems is caused by structural differences and governed by conformational equilibrium. The magnetic nonequivalence of equatorial and axial protons in substituted cyclohexanes illustrates this type. In open chain systems, magnetic nonequivalence has been attributed to hindered internal rotation and/or molecular dissymmetry. This type of nonequivalence can be induced by 1) hindered rotation about a double bond, 2) hindered rotation about a bond with partial double bond character, 3) hindered inversion of nitrogen, and 4) the presence of a near-by assymmetric center. The fourth type will be the prime concern of this present work.

Gutowsky, et. al.[45,46], have investigated the nuclear magnetic resonance spectra of substituted ethanes of the type designated as A-CX_2-B. A can be any group and B is an asymmetric or dissymetric group. This type of structure results in magnetically non-equivalent X nuclei. Several theories have been advanced to explain this phenomena. Among them are those of "conformer population", "intrinsic asymmetry", and a combination of these theories.

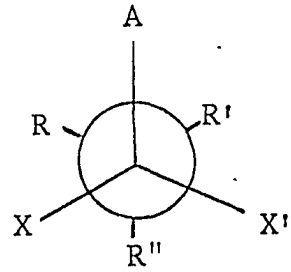
The "conformer population" theory maintains that the magnetic nonequivalence of X nuclei depends on the differences in the relative populations of the rotamers. If this is all that is involved, magnetic nonequivalence should disappear at high temperature limits because the populations should have a dependence on temperature.



CV



CVI



CVII

The "conformer population" theory does not consider, however, the dependence of the rotamers on their particular energies. Drysdale and Phillips[47], and Nais and Roberts[48], have postulated the "weighted-time-average" theory to include this energy function. This theory maintains that even with rapid interconversion among the three main rotational conformers, the residence times are not equal, for one of the geminal protons may spend longer time in a lower energy conformation. The spectrum observed is thus due to their "weighted-time-averages" over the three conformers.

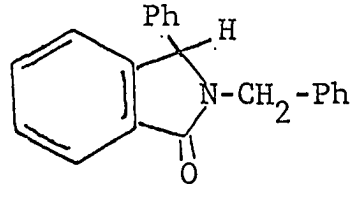
Waugh and Cotton[49] maintained that observed magnetic nonequivalence of this type could be accounted for by a symmetry argument alone. This argument was termed the "intrinsic asymmetry" theory. Lee and Sutcliffe established six symmetry classifications for substituted ethanes and prepared tables to predict the type of spectra from every combination of symmetry type, with either slow or fast rotation.[50]

Gutowsky unified these theories and applied an algebraic analysis of the various effects of conformer population and intrinsic asymmetry. Experimental techniques, however, have not yet led to satisfactory numerical evaluation of his equations.[51]

In some cases the chemical shift between the non-equivalent protons depends on the solvent. According to Snyder, it is quite possible that this variation is due to the magnetic properties of the solvent which overwhelms any smaller difference in chemical shift due to internal magnetic non-equivalence.[46]

A good example of magnetic non-equivalence of the A-CX_2-B type, occurs with 2,3-diphenylpropanoic acid (CVIII), which gives an ABX proton magnetic resonance spectrum. There are no changes in the observed spectrum on warming to 200°C or on cooling to -55°C. No changes were observed by varying the solvent over $CDCl_3$, bromobenzene, and nitrobenzene. In view of the lack of temperature dependence, it seems reasonable to propose that rapid rotation is occurring (at least at the high temperature limit). The non-equivalence thus seems to be due to an "asymmetry effect" due to intrinsic asymmetry.[52]

Levin, Lipowitz and Cohen, reported an unusually large chemical shift difference of 1.75 p.p.m. between the two benzylic protons of 1-phenyl-2-benzylphthalimidine (CIX).[53] This difference was explained on the basis of a reasonable assumption about the lowest energy conformation of CIX.



CIX

It was assumed that the conformation is as shown in Fig. 2. The N-C-C plane of the benzyl group is approximately perpendicular to the plane of the 5-membered ring. This would minimize the steric interactions between the 1- and 3-positions of the 5-membered ring and the phenyl ring of the N-benzyl group. The latter phenyl group is oriented anti to the phenyl group at C_1 and the plane of the phenyl group at C_1 is approximately perpendicular to the plane of the 5-membered ring. This eliminates steric interactions between the ortho hydrogens of this phenyl ring and the two neighboring hydrogen atoms, the benzylic hydrogen and the phenyl hydrogen at C_7. See Fig. 2.

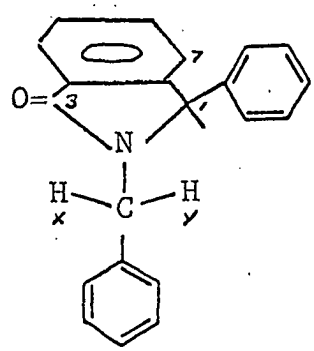
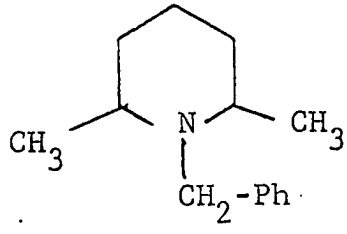


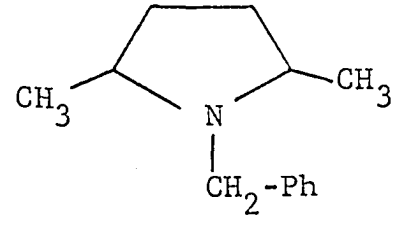
Fig. 2

In this conformation, the proton labeled X lies in the deshielding region caused by the diamagnetic anisotropy of the carbonyl group while the proton labeled Y is located in the shielding region caused by the ring current of the phenyl group at C_1. This deshielding of one proton and shielding of the other proton in addition to the intrinsic asymmetry, accounts for the large chemical shift difference.

R. K. Hill has used the phenomena of geminal magnetic non-equivalence to distinguish between cis-and trans-isomers of N-benzyl-2,6-dimethylpiperidines (CX and CXI) and N-benzyl-2,5-dimethylpyrrolidines (CXII and CXIII). The trans-isomers gave rise to non-equivalent geminal protons resulting in an AB quartet while the cis-isomers possessed benzylic protons which were equivalent and which exhibited singlets. Both cis-and trans-N-benzyl-3,4-disubstituted pyrrolidines exhibited benzylic protons as singlets. It seems that in this case the asymmetry at the 3 and/or 4 positions is too distant from the benzylic protons to perturb their magnetic environment.[32]



CX = cis
CXI = trans



CXII = cis
CXIII = trans

6. Magnetic Equivalence and Non-Equivalence of Benzylic Protons in N-Benzylpiperazines.

During the course of the present work, the 1-benzylmethylpiperazines obtained by sodium borohydride reduction of the pyrazinium salts, provided unusual examples of equivalence and non-equivalence of benzylic protons as evidenced by their n.m.r. spectra. 1-Benzyl-3-methylpiperazine (LXIII), cis-1-benzyl-3,5-dimethylpiperazine (LXIV), and cis-1-benzyl-2,3-dimethylpiperazine (LXVI), showed singlets for their benzylic protons at 3.4 p.p.m. cis-1-Benzyl-3,5-dimethylpiperidine (CXIV), produced by catalytic hydrogenation of corresponding pyridinium salt (CXXI), also showed a singlet absorption at 3.42 p.p.m. for the benzylic hydrogens. (see Table III). Trans-1-benzyl-2,5-dimethylpiperazine (LXV), however, showed an AB system centered at 3.52 p.p.m. with a chemical shift difference of 1.2 p.p.m. and a coupling constant of 14 c.p.s. (See Figures 10,11, and 12).

The fact that the benzylic protons of LXVI, with no plane of symmetry, gave a singlet while those of LXV gave a quartet of large chemical shift difference is surprising. The structures of LXVI and LXV are very similar for both have methyl groups only two atoms removed from the benzylic hydrogens. The equivalence of the hydrogens in LXVI was observed in carbon tetrachloride and benzene, so asymmetry of the molecule causes no detectable magnetic non-equivalence.

This phenomenon is very difficult to explain; however, a correlation is evident. It seems likely that an equatorial methyl group is necessary for non-equivalence and since LXV possesses a trans-configuration, both methyl groups must be equatorial as shown in Fig. 3. It would be expected that

the trans-diequatorial conformation of LXV would be theoretically favored over the trans-diaxial conformation by about 3 kilocalories per mole or an equilibrium constant of about 99.

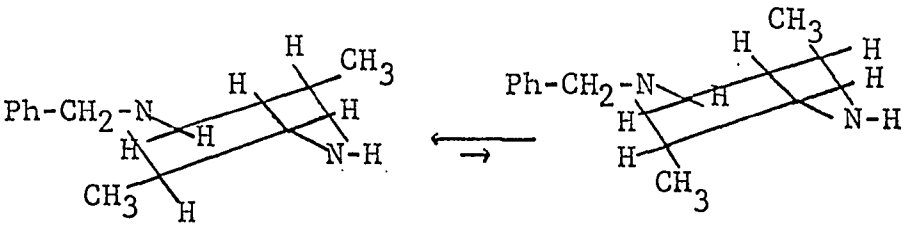


Fig. 3

The equatorial methyl by its steric interference leads to the rotational conformer with the benzyl group having the phenyl substituent away from the methyl; this being considerably more stable than that in which the methyl and phenyl are near. This in turn would result in the observed AB quartet absorption for these protons.

The singlet resonance band of the benzylic protons of LXIII, LXIV, and LXIV may be explained, as stated previously, by the fact that 3-substituents may be too far removed from the magnetic environments of the benzylic protons to perturb them and thus magnetic equivalence of these hydrogens will result.

As a result of these interesting observations, 1,4-dibenzyl piperazines were prepared and their n.m.r. spectra determined. 1,4-Dibenzyl-2-methylpiperazine (CXVI), trans-1,4-dibenzyl-2,5-dimethylpiperazine (CXVII) and cis-1,4-dibenzyl-2,5-dimethylpiperazine (CXVIII) were synthesized by treating the parent methylpiperazines with benzoyl chloride (CXIX) followed by reduction of the diamide with lithium aluminum hydride. The n.m.r. spectrum of (CXVI) showed a quartet for one set of benzylic hydrogens centered at 3.45 p.p.m. with a chemical shift difference of 0.90 p.p.m. and a

coupling constant of 14 c.p.s. The second benzyl group gave a sharp singlet at 3.31 p.p.m. Heating to 151° decreased the chemical shift difference by 0.21 c.p.s. The n.m.r. spectrum of CXVII showed a quartet centered at 3.45 p.p.m., a chemical shift difference of 1.05 p.p.m. and a coupling constant of 14 c.p.s. The benzylic hydrogens of CXVIII exhibited a quartet centered at 3.48 p.p.m. with a chemical shift difference of 0.60 p.p.m. and coupling constant of 13 c.p.s. Heating to 155° did not decrease the chemical shift difference appreciably.

The difference in chemical shift between CXVII and CXVIII is a reflection of the difference in conformer population. In CXVII, the configuration of the piperazine with two equatorial methyl groups causes a greater energy difference in the orientations of the benzylic hydrogens. In the cis-compound CXVIII, the methyl groups are flipping more rapidly and thus are only part of the time in the equatorial conformation. Thus the energy difference in the orientations of the benzylic hydrogens is not as great. (See Fig. 4).

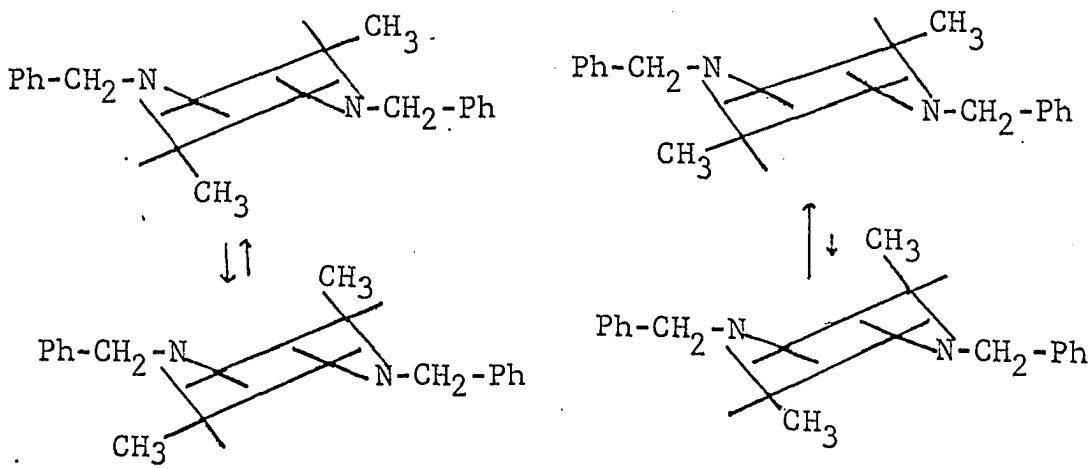


Fig. 4

It might seem at first glance that heating 1,4-dibenzyl-1-methyl piperazine CXVI, might tend to coalesce the quartet produced by the benzylic hydrogens, if the non-equivalence were due to a conformational effect. Thermodynamic calculations, however, based on data taken on methylcyclohexane (CXX) show that at high temperatures the normal 95:5 equatorial: axial ratio is perturbed only slightly by heating. For example the full energy change, ΔF, involved in going from the axial to the equatorial conformation was experimentally determined in one case to be -1.67 K cal./mole at 327°C. These values can be related to the equilibrium constant as shown below:

$$
\begin{aligned}
-\Delta F &= RT\ 2.3 \log K \\
-(-1{,}670) &= (1.99)(600)(2.3) \log K \\
1{,}670 &= 2{,}760 \log K \\
0.605 &= \log K \\
4.03 &= K \qquad \frac{4.03 \times 100}{5.03} = 80\%
\end{aligned}
$$

Thus, even at 600°K, methylcyclohexane (CXX) is 80% in the equatorial form.[54]

Thus, if CXVI behaves analogously to methyl cyclohexane, the conformational equilibrium of CXVI is not affected to a large degree by a change in temperature which in turn means that the orientations of the benzylic hydrogens should not be greatly affected by temperature. Therefore, the n.m.r. spectrum should show no appreciable coalescence.

Thus, in conclusion, an adjacent equatorial methyl group is necessary to cause non-equivalence of benzylic protons in N-benzylpiperazines.

III. EXPERIMENTAL

1. General

Melting Points: Melting points were determined using a Köfler hot-stage melting point apparatus equipped with a polarizing microscope and are uncorrected. Some melting points were determined using a Thomas Hoover capillary melting point apparatus. These are corrected.

Infrared Absorption Spectra: The infrared absorption spectra were determined using a Perkin-Elmer Model 137B infracord spectrophotometer equipped with sodium chloride optics, or using a Perkin-Elmer Model 337 grating Infrared Spectrophotometer also equipped with sodium chloride optics. The spectra determined on the Model 137B are indicated by numbers greater than one thousand, and those determined on the Model 337 are indicated by numbers less than a thousand. The spectra of liquids were determined as films, and the spectra of solids were determined as mulls in Halocarbon oil from 4000cm.$^{-1}$ to 1300 cm.$^{-1}$ and in Nujol from 1300 cm.$^{-1}$ to 650 cm.$^{-1}$. The intensity of the bands are indicated by (s), strong; (b), broad; (m), medium; and (w), weak; and the location of the bands is given in frequency units, cm.$^{-1}$.

Ultraviolet Absorption Spectra: The ultraviolet absorption spectra were determined using a Perkin-Elmer Model 4000 recording spectrophotometer. The spectra were determined in the solvents indicated and the wavelengths are given in millimicrons.

Nuclear Magnetic Resonance Spectra: The nuclear magnetic resonance spectra were determined using a Varian Model A-60 proton resonance spectrometer. The spectra were determined in the solvents indicated, and the chemical shifts are given in p.p.m. relative to tetramethylsilane as an internal standard.

Gas-Liquid Chromatographic Analysis Data: The gas chromatographic analyses were determined with a Perkin-Elmer Model 154 vapor fractometer using helium as the carrier gas. The column packing, temperature, pressure, retention times, and relative yields are indicated for each chromatogram. No calibration curves were used. The preparative scale analyses and separations were obtained by using an Aerograph autoprep Model A-700 with a 20' x 3/8" column of 20% carbowax, 20M on 6% acid washed DMCS chromosorb W. Retention times, relative yields, and compounds separated, are indicated for each chromatogram.

Analytical Data: Microanalyses were determined by Schwarzkopf Microanalytical Laboratory, Woodside, New York, and on an F and M Model 180 carbon, hydrogen and nitrogen analyzer. The dibenzylmethylpiperazines were analyzed by Dr. G. Weiler and Dr. J. B. Strauss, Microanalytical Laboratory, Oxford, England.

Preparation of 1-benzylmethylpyrazinium salt. A solution of 0.2 mole of the pyrazine and 0.2 mole of benzyl bromide in 125 ml. of acetone was heated under reflux for 2 hr. The pyrazinium salt which precipitated was removed by filtration. The filtrate was heated under reflux to cause precipitation of additional pyrazinium salt. The process was repeated to give three crops of salts. The combined yields of salt were stirred with acetone, and the suspension was separated by filtration. The solid was dried to give the pyrazinium salt in analytical purity. The following salts were obtained:[42]

1-benzyl-3-methylpyrazinium bromide (LVIII)

1-benzyl-3,5-dimethylpyrazinium bromide (LV)

1-benzyl-2,5-dimethylpyrazinium bromide (LVI)

1-benzyl-2,3-dimethylpyrazinium bromide (LVII)

Pyrazinium Bromide	Yield	M.P., °C	Formula
LVIII	50%	151-153.5	$C_{12}H_{13}BrN_2 \cdot 1/2\ H_2O$
LV	88%	246-248	$C_{13}H_{15}BrN_2$
LVI	63%	172-174.5	$C_{13}H_{15}BrN_2$
LVII	50%	162-163.5	$C_{13}H_{15}BrN_2$

Pyrazinium Bromide	Calcd. % C	Calcd. % H	Found % C	Found % H
LVIII	52.60	5.11	52.34	4.82
LV	55.94	5.42	55.95	5.50
LVI	55.94	5.42	55.87	5.72
LVII	55.94	5.42	55.78	5.36

TABLE II

Infra Red Spectra

LVIII	No. 6895:	3450(s),	1485(s),	1460(s),	1150(s),
		755(s),	730(s),	710(s),	
LV	No. 3625::	3100(s),	1495(s),	1250(s),	1150(s),
		1030(s),	770(s),	735(s),	720(s),
LVI	No. 6896:	3450(w),	3080(s),	1500(s),	1250(s),
		760(s),	740(s),	715(s),	
LVII	No. 6438:	3100(m),	1430(s),	1160(s),	770(s).

Attempted preparation of 1-benzyl-2,3,5,6-tetramethylpyrazinium bromide (LXXII). A solution of 11.2 g. of 2,3,5,6-tetramethylpyrazine (XXIV) and 12 ml. of benzyl bromide was heated under reflux in 100 ml. of acetone for 15 hr. At the end of that time no precipitation of 1-benzyl 2,3,5,6-tetramethylpyrazinium bromide (CXXII) was observed.

Reduction of the 1-benzylmethylpyrazinium salts with sodium borohydride. A 0.06 molar solution of the pyrazinium salts in 100 ml. of water was added slowly to a solution of 2.4 moles (9.1 g.) of sodium borohydride in 50 ml. of water. The mixture was stirred for 10 min. after the addition was complete, and then 10% hydrochloric acid was added until effervescence ceased. The solution was heated under reflux for 2 hr. to hydrolyze the amine-boranes, and the solution was neutralized with sodium hydroxide. Sodium chloride was added to decrease the solubility of the amine, and the mixture was extracted with ether. After drying, the ether extracts were concentrated by distillation under reduced pressure, and the residue was distilled. The following 1-benzylmethylpiperazines were obtained:[42]

1-benzyl-3-methyl piperazine (LXIII)

1-benzyl-3,5-dimethylpiperazine (cis) (LXIV)

1-benzyl-2,5-dimethylpiperazine (trans) (LXV)

1-benzyl-2,3-dimethylpiperazine (cis) (LXVI)

TABLE III

Properties of the 1-benzylmethylpiperazines

Piperazine	Yield	B.P., °C (mm)	Formula
LXIII	33%	108(2.6)	$C_{12}H_{18}N_2$
LXIV	61%	100-103(1.6)	$C_{13}H_{20}N_2$
LXV	66%	112-113(2.7)	$C_{13}H_{20}N_2$
LXVI	45%	102-103(2.5)	$C_{13}H_{20}N_2$

Piperazine	Calcd. % C	Calcd. % H	Found C	Found H
LXIII	75.74	9.54	75.79	9.79
LXIV	76.42	9.86	76.62	10.05
LXV	76.42	9.86	76.71	9.57
LXVI	76.42	9.86	76.35	9.73

TABLE IV

Infra Red Spectra

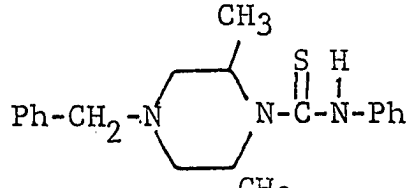
LXIII No. 4372:	3200(w),	2900(s),	2800(s),	1495(s),
	1320(s),	1150(s),	1060(s),	830(m),
	740(s),	700(s),		
LXIV No. 4965:	3200(w),	2990(s),	2800(s),	1495(s),
	1460(s),	1370(s),	1320(s),	1250(s),
	1150(s),	1070(s),	1030(s),	870(s),
	750(s),	700(s),		

TABLE IV (cont.)

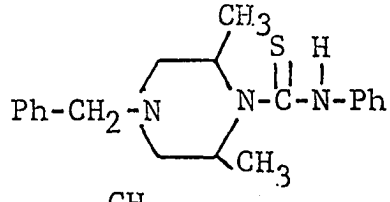
LXV No. 5255:	3300(w),	1495(s),	1450(s),	1380(s),
	1330(s),	1150(s),	1070(s),	1030(s),
	740(s),	700(s),		
LXVI No. 6648:	3300(s),	3000(s),	2800(s),	1500(s),
	1460(s),	1380(s),	1300(s),	1150(s),
	1070(s),	1030(s),	970(s),	770(s),
	740(s),	700(s).		

Preparation of phenylthioureas. The phenylthioureas were prepared following the procedure of Fuson and Shriner[55] with the following modifications. The reaction mixture was triturated with petroleum ether many times and cooling of the solution for 24 hr. was required to induce crystallization. The product was recrystallized from 95% ethanol in all cases. The yields were not determined.

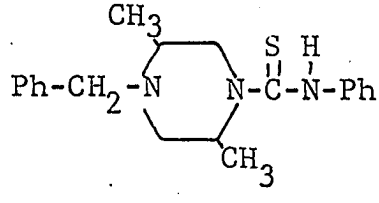
CXXIII



CXXIV



CXXV



CXXVI

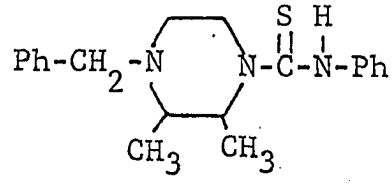


TABLE V

Properties of the Phenylthioureas

Phenyl-thioureas	M.P.,°C	Formula	Calcd. C	Calcd. H	Found C	Found H
CXXIII	130-131°	$C_{19}H_{23}N_3S$	70.12	7.12	70.08	7.23
CXXIV	126-127°	$C_{20}H_{25}N_3S$	70.75	7.42	70.95	7.45
CXXV	114-115°	$C_{20}H_{25}M_3S$	70.75	7.42	71.03	7.39
CXXVI	145-145.5°	$C_{20}H_{25}N_3S$	70.75	7.42	70.95	7.31

TABLE VI

Infra Red Spectra

CXIII No. 4964:	3300(s),	2800(w),	1520(s),	1450(s),
	1330(s),	1050(s),	760(s),	700(s),
CXIV No. 94:	3300(s),	2950(w),	2800(w),	1600(s),
	1520(s),	1270(s),	1060(s),	710(s),
	690(s),			
CXV No. 184:	3230(s),	2950(w),	2800(w),	1600(s),
	1520(s),	1300(m),	1260(s),	1230(s),
	1170(s),	1090(s),	1060(s),	700(s),
CXVI No. 6658:	3300(s),	3000(s),	1520(s),	1340(s),
	1330(s),	1290(s),	1170(s),	1095(s),
	740(s),	700(s).		

Purification of trans-1-benzyl-2,5-dimethylpiperazine (LXV). A 5 g. portion of the picrate derivative (m.p. 224-226°) of trans-1-benzyl-2,5-dimethylpiperazine (CXXX) was recrystallized 3 times from 95% ethanol. The final product which was recovered melted from 234 to 236°. This picrate (CXXX) was dissolved in base, and the solution was extracted with ether. The solution was concentrated under reduced pressure and 0.2 ml. of trans-1-benzyl-2,5-dimethylpiperazine (LXV) was recovered as a residue. This product was analyzed by gas liquid chromatography and was found to contain two components in a ratio of 99 to 1. The predominant compound was shown to be the trans-isomer of LXV by the debenzylation reaction to be described.

I. R. No. 5455: (Same as No. 5255).

Debenzylation of cis-1-benzyl-3,5-dimethylpiperazine (LXIV). A suspension of 1.2 g. of 5% Pd/C and 4.8 g. of cis-1-benzyl-3,5-dimethylpiperazine (LXIV) in 100 ml. of 95% ethanol was prepared in a filter flask fitted with a balloon attached to the side opening and being magnetically stirred. The flask was stoppered with a rubber stopper carrying a three-way stopcock. This stopcock provided for introduction and release of hydrogen. The flask was flushed with hydrogen three times, the stirrer was started, and the solution stirred until the balloon ceased to collapse. The solution was filtered, and the ethanol removed by distillation. A white solid (0.4 g. 15%) remained as residue and was identified as cis-2,6-dimethylpiperazine, (XCIII), m.p. 114-115° (lit.[34], m.p. 115-116°).

I. R. No. 5798: 3300(s), 3000(s), 2800(s), 1450(s); 1130(s), 1030(s), 960(s), 890(s), 830(s).

Debenzylation of trans-1-benzyl-2,5-dimethylpiperazine (LXV). A solution of 5.1 g. of trans-1-benzyl-2,5-dimethylpiperazine (LXV) from the sodium borohydride reduction of the corresponding pyrazinium salt was prepared in 50 ml. of 95% ethanol. The solution was hydrogenated over 3 g. of Pd/C (5%) in the manner described previously. The solution was filtered and divided into two equal parts. To one part was added a saturated solution of picric acid. The resultant precipitate was recrystallized twice from ethanol to give 1 g. of picrate (CXXVII), m.p. 306-307° (dec.) corr. The decomposition point of an authentic sample of the picrate of trans-2,5-dimethylpiperazine (CXXVII) was 308-309° corr. A picrate derivative of an authentic sample of cis-2,5-dimethylpiperazine (CXXVIII) decomposed at 272-273° corr.[59]

The solvent was removed from the second half of the above solution by distillation. The residue was purified by sublimation to give 0.2 g. (17%) of a white solid, m.p. 113.5-115.5°. The melting point of an authentic sample of trans-2,5-dimethylpiperazine (XCII) was 114.5-116.8°. The mixture melting point was 114.7-116.2°. The infrared spectra of the product and of an authentic sample were superimposable.

XCII I. R. No. 6048: (trans product) and No. 5982 (trans sample)
3300(s), 2900(s), 2800(s), 1450(w), 1250(s), 1160(s), 1070(s), 1000(s), 950(s), 890(s), 830(s).

CXXIX I. R. No. 5982: (cis sample)
3300(s), 2900(s), 2800(s), 1450(s), 1380(s),
1320(s), 1150(s), 920(b), 880(b), 770(b).

Debenzylation of cis-1-benzyl-2,3-dimethylpiperazine (LXVI). A solution of 0.8 g. of cis-1-benzyl-2,3-dimethylpiperazine (LXVI), from the sodium borohydride reduction of the corresponding pyrazinium salt LVII, in 50 ml. of 95% ethanol was hydrogenated over 0.5 g. of Pd/C (5%) for 1 hr. in the manner described previously. The solution was filtered and divided into two equal parts. The first part was concentrated but no residue remained.

The second part was treated with a saturated solution of picric acid, and 1 g. of picrate (XCIV), (m.p. 274-275° corr.) precipitated. The melting point of the picrate of cis-2,3-dimethylpiperazine (XCI) is reported at 287°.[41] The picrate was dissolved in 50 ml. of 5% sodium hydroxide solution and treated with 3 ml. of benzenesulfonyl chloride. An oily precipitate remained and solidified after standing overnight. The disulfonamide (XCV) was removed by filtration, washed thoroughly with 5% sodium hydroxide, and recrystallized from 95% ethanol. The disulfonamide (XCV), (0.1 g. 14%) was obtained as a white crystalline solid m.p. 144-145.5° corr. (lit.[41], cis, 142.5-143.5°, trans 217-218°).[57]

I. R. No. 6885: 1450(s), 1350(s), 1280(s), 1030(s),
1000(s), 935(s), 870(s), 840(s),
740(s), 690(s).

Anal. Calcd. for $C_{18}H_{22}N_2O_4S_2$: C, 54.78; H, 5.62. Found: C, 55.10; H, 5.64.

Preparation of 1-benzyl-3-carboxamidopyrazinium bromide (LXI). A solution of 12.3 g. of pyrazinamide (XLIV) and 12 ml. of benzyl bromide in 300 ml. of 2-propanol was heated under reflux 2 hr., and the reaction mixture was allowed to stand overnight. A precipitate formed and was removed by filtration. The filtrate was evaporated to a small volume and more solid precipitated. The filtrate from the second crop on further evaporation gave only a tarry residue. The total precipitate was washed with an acetone-ether (3:1) solution and recrystallized from 2-propanol to give 3.6 g. (8.2%) of a solid (m.p. 167-168°) tinged with yellow.

I.R. No. 5028: 3300(b), 1690(s), 1190(s), 1150(s), 1090(s), 1030(s), 880(s), 780(s), 730(b), 710(s).

Anal. Calcd. for $C_{12}H_{12}BrNO$: C, 46.86; H, 4.22.
Found: C, 46.73; H, 4.40.

Preparation of hexamethylenetetramine (XLI). Hexamethylenetetramine was prepared by using a modification of the method reported by Adams and Johnson.[56] A solution of 400 ml. of concentrated ammonium hydroxide and 200 ml. of 40% formaldehyde solution was stirred and allowed to evaporate overnight. A white crystalline solid (61.4 g., 16.4%) m.p. 262-263° (lit.[56], 263°) was obtained.

I.R. No. 6478: 2900(s), 1460(s), 1370(s), 1240(s), 1050(s), 1000(b), 820(s), 660(s).

Preparation of the salt of hexamethylenetetramine and α-bromoacetophenone (XLII). A solution of 24 g. of α-bromoacetophenone (XL) in 20 ml. of chloroform was added with stirring to a solution of 17.5 g. of hexamethylenetetramine in 100 ml. of hot chloroform. A precipitate formed almost immediately giving 38.8 g. (95%) of a powdery solid m.p. 167-169° (lit.[20], 165°).

I.R. No. 6574: 2950(s), 1700(s), 1280(s), 1220(s), 1150(s), 1060(s), 1010(s), 940(s), 835(s), 800(s), 760(s), 680(s).

Preparation of the mixture of α-amino acetophenone hydrochloride and hydrobromide salts (XLIII). A solution of 38.7 g. of the salt of hexamethylenetetramine (XLII) and α-bromoacetophenone (XL) and 38.7 ml. of concentrated hydrochloric acid in 310 ml. of 95% ethanol was allowed to stand at room temperature for 3 days with occassional shaking. The solution was filtered and the filtrate was concentrated under reduced pressure. The residue was recrystallized from 10 ml. of water to give 15.7 g. (63.5%) of a brown crystalline solid, m.p. 196-206°, as product. The yield was calculated on the premise that the product was primarily α-aminoacetophenone hydrobromide (CXXXI), lit.[20] m.p. 217-218°.

I.R. No. 6519: 2800(s), 1690(s), 1500(s), 1250(s), 970(s), 905(s), 770(s), 690(s).

Preparation of 2,5-Diphenylpyrazine (XXXI). A solution of 15.7 g. of the crude XLIII from above and 23 ml. of concentrated ammonium hydroxide in 60 ml. of 95% ethanol was heated under reflux open to the air for 12 hr. The yellow precipitate which formed was removed by filtration and recrystallized from 95% ethanol to give 4.3 g. (50.6%)

of a yellow crystalline solid, m.p. 196.8-197.8° (lit.[22] m.p. 195-196°).

I.R. No. 6546: 1480(s), 1470(s), 1180(s), 1020(s), 920(s), 760(s), 690(s).

Preparation of 1-methyl-2,5-diphenylpyrazinium bromide (LIX). A solution of 4.6 g. of 2,5-diphenylpyrazine (XXXI) and 10 ml. of methyl iodide in 25 ml. of dimethylformamide was heated under reflux for 4 hr. An additional 10 ml. of methyl iodide was added, and the solution was heated for another 4 hr. The solution was cooled, and a large excess of ether was added. The precipitate which resulted was removed by filtration, and the residue was dissolved in 50 ml. of methanol. The methanol solution was then treated with ether, and the resulting precipitate was collected by filtration to give 4.8 g. (65%) bright yellow crystals. The material changed color, melted, and resolidified slowly over a wide range on heating to give the melting point of 2,5-diphenylpyrazine (XXXI) 193-196°.

I.R. No. 6629: 3000(m), 1480(s), 1450(s), 1380(s), 1200(s), 1150(s), 780(s), 770(s), 750(m), 700(s).

Anal. calcd. for $C_{12}H_{15}IN_2$: C, 54.56; H, 4.04. Found: C, 54.75; H, 3.80.

Preparation of 5,6-dihydro-2,3-diphenylpyrazine (XXXIX). A solution of 38.8 g. of benzil (XXXVII) and 12.8 ml. of ethylene diamine (XXXVIII) in 60 ml. of 95% ethanol was heated to boiling on a steam bath. Almost immediately a precipitate formed. The heating was continued for 15 min. and the solution was allowed to stand overnight. The product was isolated by filtration to give 38.5 g. (89.2%) of 5,6-dihydro-2,3-diphenylpyrazine (XXXIX) m.p. 152-157.2° corr. (lit.[19], 160-161°).

I.R. No. 6505: 2995(w), 1560(s), 1440(s), 1280(s), 1030(s), 990(s), 930(s), 860(m), 800(s), 770(s), 730(s), 710(s).

Preparation of 2,3-diphenylpyrazine (XXX). A 20 g. portion of the above impure 5,6-dihydro-2,3-diphenylpyrazine (XXXIX) was heated to the melting point in a stream of air under reduced pressure for 23 min. The melt was allowed to cool and then was poured into concentrated hydrochloric acid. The solution was filtered through a sintered glass funnel, and the filtrate was neutralized with potassium hydroxide. The resultant precipitate was removed by filtration and redissolved in concentrated hydrochloric acid. The solution was treated with animal charcoal, heated to boiling, and filtered. This animal charcoal treatment was repeated twice and the color of the solution lightened considerably. The solution was again neutralized and 5.6 g. (28.3%) of 2,3-diphenylpyrazine (XXX), m.p. 119-121.5° (lit.[19], 118-119°C), were obtained.

I.R. No. 6573: 3000(w), 1390(s), 1150(s), 1100(s), 1020 1020(s), 770(s), 700(s).

Preparation of 2,3-diphenyl-1-methylpyrazinium iodide (LX). A solution of 8.0 g. of 2,3-diphenylpyrazine (XXX) and 20 ml. of methyl iodide in 200 ml. of 95% ethanol was heated under reflux on a steam bath overnight. The solution was cooled, treated with ether, and allowed to stand in an ice bath. The precipitate which resulted was removed by filtration, and 4.7 g. (27.4%) of orange crystalline methiodide, m.p. 197-198°, was obtained.

I.R. No. 6590: 3000(w), 1420(s), 1230(s), 1150(s), 850(s), 800(s), 770(s), 720(s).

Anal. calcd. for $C_{12}H_{15}IN_2$: C, 54.56; H, 4.04. Found: C, 54.10; H, 4.02.

Preparation of 2,3-dimethylquinoxaline (XXXV). A solution of 135 g. of o-phenylenediamine (XXXIV) was prepared in 2 L. of acetic acid at 65°. A solution of 107.6 g. of 2,3-butanedione (XXXIII) in 750 ml. of water was added with stirring. The mixture was stirred an additional 15 min. and allowed to sit in ice for 2 hr. The crude 2,3-dimethylquinoxaline (XXXV) which precipitated was removed by filtration and dried, and 183.6 g. (93.0%), (m.p. 106.5-107°, lit.[18], 105.5-106.5) of a light tan product was obtained.

Preparation of 2,3-dimethylpyrazine (XXIX). In a 3 L. beaker, 40 g. of 2,3-dimethylquinoxaline (XXXV) were dissolved in 2 L. of water at 80°. Potassium permanganate (240 g.) was added in portions with vigorous stirring at such a rate as to maintain the temperature at 85°. The addition required 1 hr. The reaction mixture was then stirred another hour at 90°. The hot mixture was filtered, and the cake of insoluble manganese dioxide was washed with hot water. The combined filtrate and washings were evaporated to about 1 L. under reduced pressure, and 126 ml. of 37% hydrochloric acid were added with stirring. Evaporation under reduced pressure was continued until 500 ml. of solution remained. The remaining solvent was removed by evaporation in a stream of air. To the residue was added 50 ml. of water and 750 ml. of acetone. The mixture was heated under reflux for 15 min. and filtered, and the filtrate was allowed to evaporate to dryness. The resudue was then re-

crystallized once from water to give 23.7 g. (47.7%) of very crude 5,6-dimethylpyrazine-2,3-dicarboxylic acid (XXXVI), m.p. 170-191° (lit.[18], 192-193°).

I.R. No. 6513: 3500(s), 2400(b), 2000(b), 1700(s), 1430(s), 1380(s), 1280(b), 1130(b), 790(s), 740(s).

This material was not purified further and was dissolved in 125 ml. of quinoline. The solution was heated under reflux for 4 hr. and the liquid reaction mixture was fractionally distilled. 2,3-Dimethylpyrazine (XXIX) 4.7 g. (17.2%) was obtained as a clear colorless liquid, b.p. 66-68°, 20 mm.

I.R. No. 6561: 3400(w), 3050(s), 1530(s), 1405(s), 1250(s), 1180(s), 1030(s), 970(s), 720(m).

Preparation of 1,2,3,5,6-pentamethylpyrazinium iodide (LIV). A solution of 13.6 g. of 2,3,5,6-tetramethylpyrazine (XXIV) and 32 ml. of methyl iodide in 100 ml. of acetone was heated under reflux for 24 hr. The solution was concentrated to a small volume and cooled. The solution was treated with ether and 9.8 g. (35.2%) of the methiodide, m.p. 220-221° were obtained.

I.R. No. 6888: 1480(s), 1280(s), 1210(s), 990(s), 820(s), 730(b), 680(m).

Anal. calcd. for $C_9H_{15}IN$: C, 38.87; H, 5.44. Found: C, 39.31; H, 5.65.

Reduction in the ultraviolet spectrophotometer cell. The sample cell was filled with a solution of appropriate concentration of the pyrazinium salt. A portion of solid sodium borohydride of no greater weight than .05 g. was inserted directly into the cell by means of a surgical knife.

The reference and sample cell doors were closed immediately, and the drum was rotated at the maximum forward speed in order to record the absorption of all the possible intermediates. Some curves of the reductions are shown in Figs. 5 to 9 . The maxima are listed in Table IV.

Attempted reduction of 1-benzyl-3-carboxamidopyrazinium bromide (LXI). A solution of 5.9 g. of 1-benzyl-3-carboxamidopyrazinium bromide (LXI) in 50 ml. of water was slowly added to a solution of 3.0 g. of sodium borohydride in 150 ml. of water. After the addition was completed, the solution was stirred another 10 min. The solution was extracted with ether, and the ether was removed under reduced pressure. An infrared spectrum was taken of the tarry residue. Although the spectrum was of poor quality, it did show the absence of B-H stretching bands. All attempts to crystallize the residue or prepare a solid derivative failed.

I.R. No. 5136: 3400(b), 3000(s), 1700(b), 750(b), 700(b).

Attempted reduction of 1-methyl-2,5-diphenylpyrazinium bromide (LIX). Method A. A solution of 4 g. of 1-methyl-2,5-diphenylpyrazinium bromide (LIX) in 200 ml. of 95% ethanol was added with stirring and cooling in an ice bath to a flask containing 2 g. of solid sodium borohydride. After the addition was completed, the solution was stirred for an additional 0.5 hr. The ethanol was removed by evaporation, and the residue was treated with water and extracted with ether. The ether was removed by evaporation under reduced pressure, and a tarry residue was obtained. The infrared spectrum of this residue showed carbonyl absorption. The residue was treated with petroleum ether, ethanol, and acetone in an attempt to induce crystallization, but without success.

I.R. No. 6735: 3400(s), 3100(s), 2900(s), 1700(s), 930(s), 760(b), 700(b).

Method B. The procedure and results are essentially the same as in Method A, with the exception that 4 ml. of acetic acid were added to the 200 ml. ethanol solution of 4 g. of 1-methyl-2,5-diphenylpyrazinium bromide (LIX) before the reaction with 2 g. of sodium borohydride. The infrared spectrum of the tarry product again showed carbonyl absorption.

I.R. No. 7119: 3500(b), 1680(s), 1500(s), 1450(s), 1120(s), 760(b), 700(b).

Attempted reduction of 1-methyl-2,3-diphenylpyrazinium bromide (LX). Method A. A solution of 4 g. of 1-methyl-2,3-diphenylpyrazinium bromide (LX) in 200 ml. of 95% ethanol was cooled in an ice bath. Sodium borohydride (2.0 g.) was added slowly to this solution with stirring. The stirring was continued another 1.5 hr. The ethanol was removed by evaporation, and the residue was treated with water and extracted with ether. The ether was concentrated by evaporation and the tarry residue was treated with petroleum ether, acetone, and ethanol in order to induce crystallization. All attempts failed. The infra-red spectrum No. 6929 of the residue showed bands indicative of carbonyl groups. The residue was dissolved in ethanol and treated with a saturated solution of picric acid. A black tarry precipitate developed which was discarded.

I.R. No. 7191: 3500(b), 3100(s), 1650(b), 1500(s), 1410(s), 760(b), 710(b).

Method B. The procedure and results are essentially the same as in Method A, with the exception that 5 ml. of acetic

acid were added to the 200 ml. ethanol solution of 4 g. of 1-methyl-2,3-diphenylpyrazinium bromide (LX) before the reaction with 2 g. of sodium borohydride. The infrared spectrum of the tarry product again showed absorption suggestive of carbonyl groups.

I. R. No. 7191: 3500(b), 3100(s), 1650(b), 1500(s), 1410(s), 760(b), 710(b).

Attempted reduction of 1,2,3,5,6-pentamethylpyrazinium iodide (LIV). Method A. A solution of 6 g. of 1,2,3,5,6-pentamethylpyrazinium iodide (LIV) in 50 ml. of water was added slowly to a solution of 2 g. sodium borohydride in 100 ml. of water which was cooled in an ice bath. The addition took 5 min., and the stirring was continued another 10 min. Concentrated hydrochloric acid was added until effervescence ceased. The solution was heated under reflux for 1 hr. and evaporated to a small volume. The solution was neutralized and allowed to evaporate to dryness. The residue was extracted with acetone. The acetone solution was evaporated, and the liquid residue was distilled. The liquid in the distilling flask solidified, however, on being heated under reduced pressure.

The infrared spectrum of this solid showed absorption which appeared to be due to carbonyl groups. The residue was dissolved in 5% base and treated with an excess of p-toluenesulfonyl chloride. This solution was then treated with concentrated ammonium hydroxide in order to hydrolyze the excess p-toluenesulfonyl chloride. No precipitate remained after this treatment. The solution was treated with phenylisothiocyanate and stirred for several hours. No precipitate formed. The solution was discarded.

I. R. No. 6860: 3600(b), 3000(s), 2000(b), 1650(b), 1460(s), 1390(s), 1170(b).

Method B. A solution of 3 g. of 1,2,3,5,6-pentamethylpyrazinium iodide (LIV) in 50 ml. of water was added slowly to a stirred solution of 2 g. of sodium borohydride in 100 ml. of water which was cooled in an ice bath. The addition was completed in 5 min., and the stirring was continued another 10 min. Concentrated hydrochloric acid was added until effervescence ceased. The acidic solution was evaporated to less than 50 ml. volume, and base was added. The solution was extracted with ethyl acetate. The ethyl acetate extracts were evaporated under reduced pressure but gave no residue. The water solution was saturated with sodium carbonate until the solution became thick. The emulsion was extracted with chloroform, and the chloroform extracts were evaporated under reduced pressure to a small volume. The solution was analyzed by gas-liquid chromatography, but no peaks were found. The sodium carbonate emulsion was extracted with acetone. The acetone extracts were concentrated under reduced pressure to a small volume and added to the chloroform extract. The solutions were concentrated to a very small volume and again analyzed by gas-liquid chromatography. Several peaks with long retention times were evident. (See Table VI). All solvent was removed by evaporation under reduced pressure and an infrared spectrum of the residue was determined. Absorptions indicative of carbonyl groups were evident. The usual attempts at crystallization were unsuccessful.

I. R. No. 6856: 3500(b), 2000(w), 1610(b), 970(b), 730(s).

Preparation of the dibenzoyl derivative of methyl substituted piperazines. A solution of 0.05 moles of the methyl substituted piperazine and 15 g. of benzoyl chloride was prepared in 20 ml. of water. The solution was stirred slowly while 80 ml. of 5% sodium hydroxide were added in small amounts. The solution was stirred vigorously for 0.5 hr. and the precipitate which formed was removed by filtration. The residue from the filtration was stirred for 2 hr. in fresh 5% sodium hydroxide and removed by filtration and dried. The following dibenzyl derivatives were obtained.

Trans-1,4-dibenzoyl-2,5-dimethyl piperazine (CXXXII)

Cis-1,4-dibenzoyl-2,5-dimethyl piperazine (CXXXIII)

1,4-dibenzoyl-2-methyl piperazine (CXXXIV)

Dibenzoyl piperazine	Yield	M.P.	lit. M.P.
CXXXII	62.2%	229-231°	230-231°[57]
CXXXIII	51.4%	145-145.5°	147-148°[57]
CXXXIV	84.9%	146.5-148.5°	145.5-146.5[57]

Infra-red Spectra

(CXXXII) No. 7014:	2980(s),	1620(s),	1600(s),	1430(s),
	1330(s),	1270(s),	1200(s),	1160(s),
	1105(s),	1060(s),	950(s),	930(s),
	840(s),	780(s),	745(s),	710(s),
	660(s).			
(CXXXIII) No. 6968:	2980(w),	1630(s),	1620(s),	1420(s),
	1280(s),	1210(s),	1060(s),	800(s),
	740(s),	730(s),	705(s).	

(CXXXIV) No. 7228: 2980(w), 1640(s), 1602(s), 1500(s), 1470(s), 1440(s), 1240(s), 1170(s), 1100(s), 1050(s), 1030(s), 770(s), 755(s), 710(s), 660(s).

Preparation of 1,4-dibenzylmethyl piperazines. An emulsion of 0.01 mole of 1,4-dibenzoyl-methyl piperazine in 50 ml. of anhydrous ether was slowly added with stirring to a slurry of 3 g. of lithium aluminum hydride in 100 ml. of anhydrous ether. The resulting emulsion was heated under reflux for 48 hr. An ether-water mixture and 10% sodium hydroxide solution were then added to decompose the excess lithium aluminum hydride. The resulting solution was shaken vigorously in a separatory funnel, the ether layer was removed, and concentrated under reduced pressure. The solid residue was recrystallized from ether. The following dibenzyl derivatives were obtained.

trans-1,4-dibenzyl-2,5-dimethyl piperazine (CXVII)
cis-1,4-dibenzyl-2,5-dimethyl piperazine (CXVIII)
1,4-dibenzyl-2-methylpiperazine (CXVI)

Dibenzylmethyl piperazine	Yield	M.P.	lit. m.p.
CXVII	81.5%	107-109°	105-106°[58]
CXVIII	64.6%	56-60°	—
CXVI	89.2%	picrate 276°	—

Dibenzyl-Methyl Piperazine	Formula	Anal. calcd. C	H	Found C	H
CXVII	$C_{20}H_{26}N_2$	-	-	-	-
CXVIII	$C_{20}H_{26}N_2 \cdot 1/2\ H_2O$	79.30	8.91	79.45	9.10
CXVI	$C_{19}H_{24}N_2$	81.38	8.62	81.28	8.64

Infra-red Spectra

(CXVII) No. 7047: 2980(w), 2800(m), 1500(s), 1460(s), 1380(s), 1330(s), 1280(s), 1240(s), 1180(s), 1080(s), 1030(s), 980(s), 850(s), 750(s), 740(s), 700(s).

(CXVIII) No. 7008: 3550(s), 3050(s), 3000(s), 2800(s), 1600(s), 1500(s), 1450(s), 1380(s), 1285(s), 1150(s), 1080(s), 1040(s), 980(s), 920(s), 870(s), 840(s), 740(s), 700(s).

(CXVI) No. 7413: 3010(s), 3000(s), 2800(s), 1603(w), 1500(s), 1470(s), 1180(s), 1060(s), 1040(s), 930(s), 850(s), 740(s), 710(s).

Preparation of 3-cyanopyrazine (XXXII). A mixture of 24.6 g. of pyrazinamide (XLIV) and 28.4 of phosphorous pentoxide was heated under reduced pressure in a distillation apparatus, and a clear liquid contaminated with sublimed pyrazinamide (XLIV) was collected as distillate. The crude distillate was redistilled from phosphorous pentoxide until the absorption band at 1700 $cm.^{-1}$ in the infrared spectrum disappeared. The liquid was redistilled to give 5.7 g. (27.1%) of a clear colorless liquid, b.p. 107°, 24 mm. (lit.[23], 87°, 6 mm).

I. R. No. 7054: 3010(w), 2250(s), 1470(s), 1400(s), 1300(s), 1230(s), 1180(s), 1060(s), 1030(s), 870(s), 760(s).

Preparation of 3-cyano-1-methylpyrazinium methylsulfonate (LXII). A solution of 1 ml. of 3-cyanopyrazine (XXXII) and 4 ml. of dimethyl sulfate in 10 ml. of benzene was allowed to stand at room temperature for 4 hr. A precipitate of white crystals was removed by filtration, washed thoroughly with petroleum ether, and dried to give 0.4 g. (18.2%) of 3-cyano-1-methyl pyrazinium methanosulfate (LXII), m. p. 128.5-131.5°.

I. R. No. 7621: 3020(s), 3000(s), 2950(s), 2300(w), 1480(s), 1230(b), 1140(s), 1080(s), 1010(b), 870(s), 760(b), 730(w).

Anal. Calcd. for $C_7H_9N_3O_4S$: C, 36.36; H, 3.92. Found: C, 36.56; H, 3.97.

Preparation of 1-benzyl-3,5-dimethylpyridinium bromide monohydrate (CXXI). A solution of 10.7 g. of 3,5-lutidine (CXXXV) and 17.1 g. of benzyl bromide was prepared in 10 ml. of acetone. An exothermic reaction occurred almost immediately and resulted in the precipitation of a hygroscopic white solid, which was removed by filtration and recrystallized from 2-propanol to give 18.7 g. (63.2%) of CXXI, m.p. 195.5-198.5°.

I. R. No. 7198: 3500(s), 3000(m), 1500(s), 1200(s), 1130(s), 1030(b), 970(b), 940(s), 890(s), 840(b), 780(s), 730(s), 690(s).

Anal. Calcd. for $C_{14}H_{18}BrNO$: C, 56.75; H, 5.43. Found: C, 57.62; H, 5.42.

Preparation of cis-1-benzyl-3,5-dimethylpiperidine (CXIV). Method A. To a cooled, well-stirred solution of 5.56 g. of 1-benzyl-3,5-dimethylpyridinium bromide monohydrate (CXXI), 15 g. of potassium carbonate, 10 ml. of methanol, and 90 ml. of water was added 2 g. of sodium borohydride. The solution was stirred 1.5 hr. and then extracted with ether. The ether extracts were evaporated under reduced pressure, and the residue, 2.9 g., was examined by gas-liquid chromatography. (See Table VI). The chromatogram showed 5 peaks of long retention time. The infrared spectrum showed two absorption bands in the 1600-1750 $cm.^{-1}$ carbonyl region.

I. R. No. 7209: 2900(b), 1705(s), 1680(s), 1500(s), 1460(s), 1300(s), 1280(s), 1200(b), 1150(s), 1090(s), 1030(s), 840(b), 750(b), 700(b).

To a solution of this residue in 80 ml. of 95% ethanol was added 0.03 g. of platinum oxide and the emulsion was subjected to hydrogenation in the apparatus and manner described previously. The hydrogenation was allowed to continue for 2 hr. Excess hydrogen was released and the solution allowed to stir overnight. The ethanol was removed by evaporation under reduced pressure, and 1.8 g. of residue was obtained. The gas-liquid chromatogram of this residue showed 3 peaks and a shoulder. The components responsible for the major peak and shoulder were isolated by using the preparative gas-liquid chromatograph. (See Table V). The main component was shown to be cis-1-benzyl-3,5-dimethyl piperidine (CXIV). A sufficient amount of the product (0.5 g.)

was isolated for the nuclear magnetic resonance study.

I. R. No. 7202: 3000(s), 2800(s), 1470(s), 1390(s), 1300(s), 1140(s), 1080(s), 1030(s), 890(s), 750(b), 710(s).

Anal. Calcd. for $C_{14}H_{21}N$: C, 82.70; H, 10.41. Found: C, 82.90; H, 10.70.

Method B. A solution of 5 g. of 1-benzyl-3,5-dimethylpyridinium bromide monohydrate (CXXI) in 100 ml. of 95% ethanol was treated with hydrogen over 0.2 g. platinum oxide using the method described previously. The hydrogenation was stopped after 2 hr. and the ethanol was evaporated under reduced pressure. The residue was dissolved in 10% sodium hydroxide solution and extracted with ether. The ether extracts were evaporated under reduced pressure and the residue (2.1 g.) was analyzed by gas-liquid chromatograph. The chromatogram showed 3 peaks (See Table VI). The two major components were separated and isolated using the preparative gas-liquid chromatograph (See Table V). The component present in greatest amount was identified as cis-1-benzyl-3,5-dimethyl piperidine (CXIV).

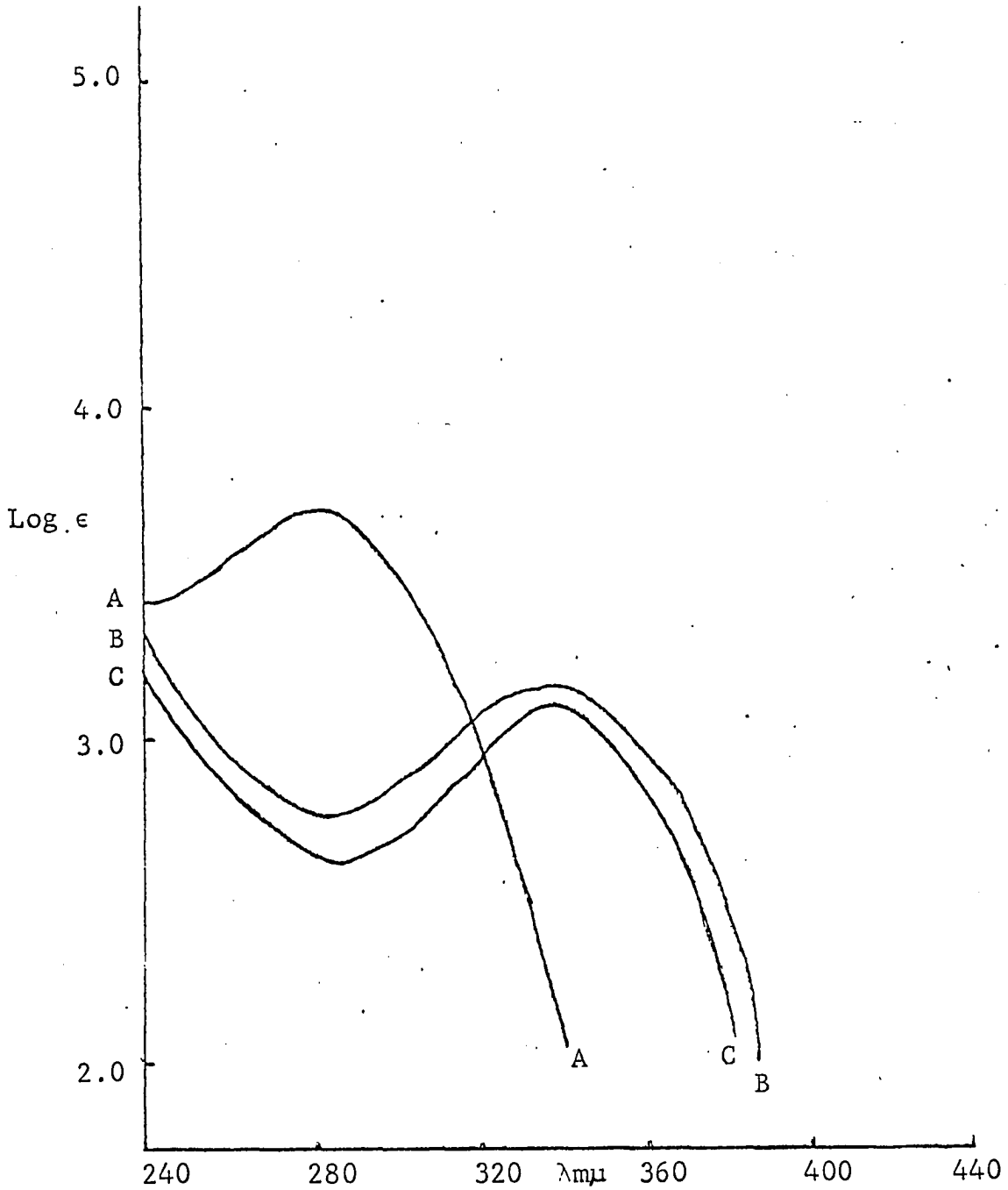
I. R. No. 7211: 3000(s), 2800(s), 1470(s), 1390(s), 1300(s), 1140(s), 1080(s), 1030(s), 890(s), 750(b), 710(s).

Anal. Calcd. for $C_{14}H_{21}N$: C, 82.70; H, 10.41. Found: C, 82.65; H, 10.26.

The picrate (CXXXVI) was prepared in ethanol and after recrystallization, melted at 144.5-146.5°.

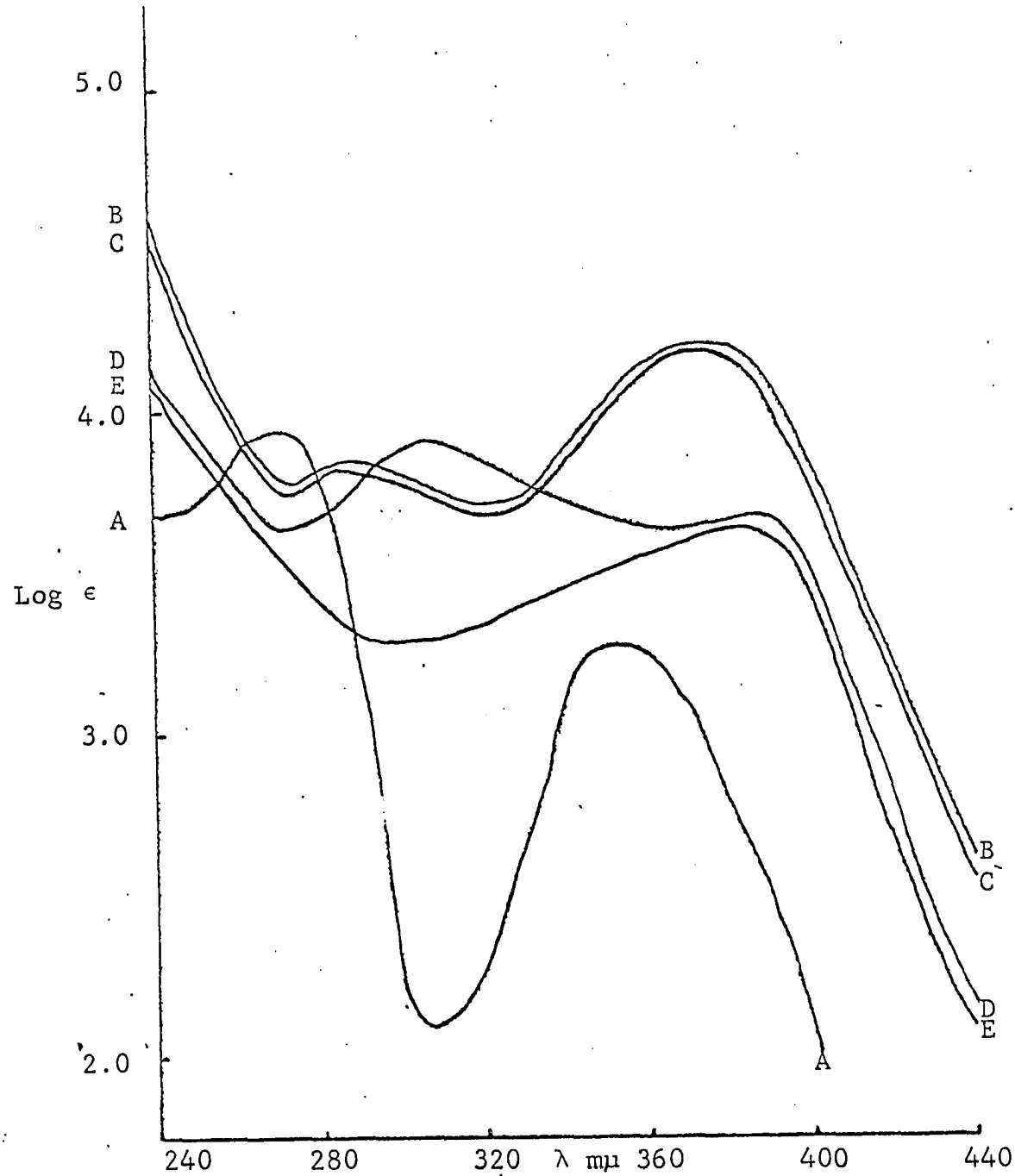
ULTRA-VIOLET SPECTRA

Fig. 5



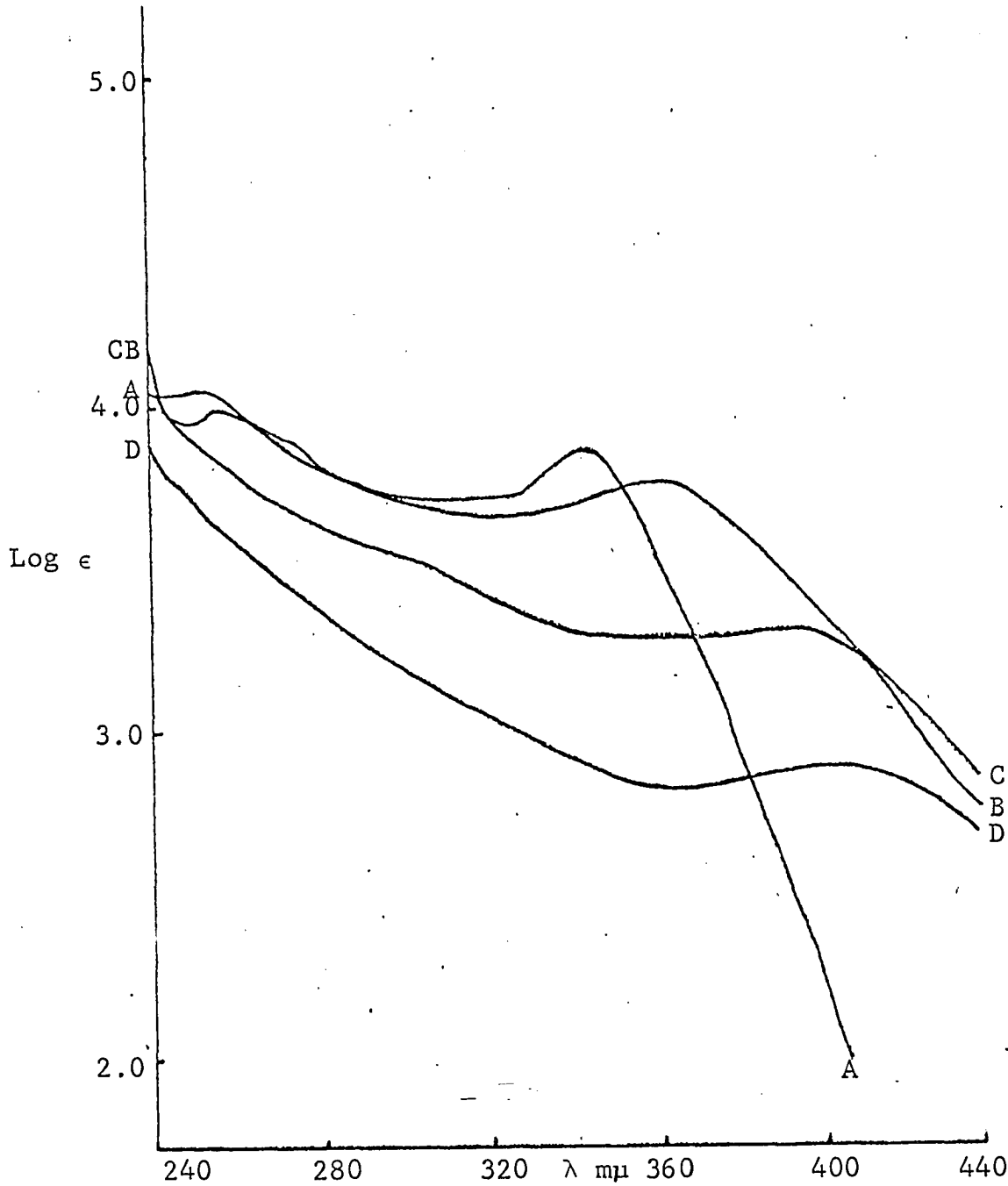
A = 1-Benzyl-3,5-dimethylpyrazinium bromide in 2-propanol
B = First spectrum observed after addition of sodium borohydride
C = Second spectrum observed after addition of sodium borohydride. No absorption was noted after addition of acid

Fig. 6



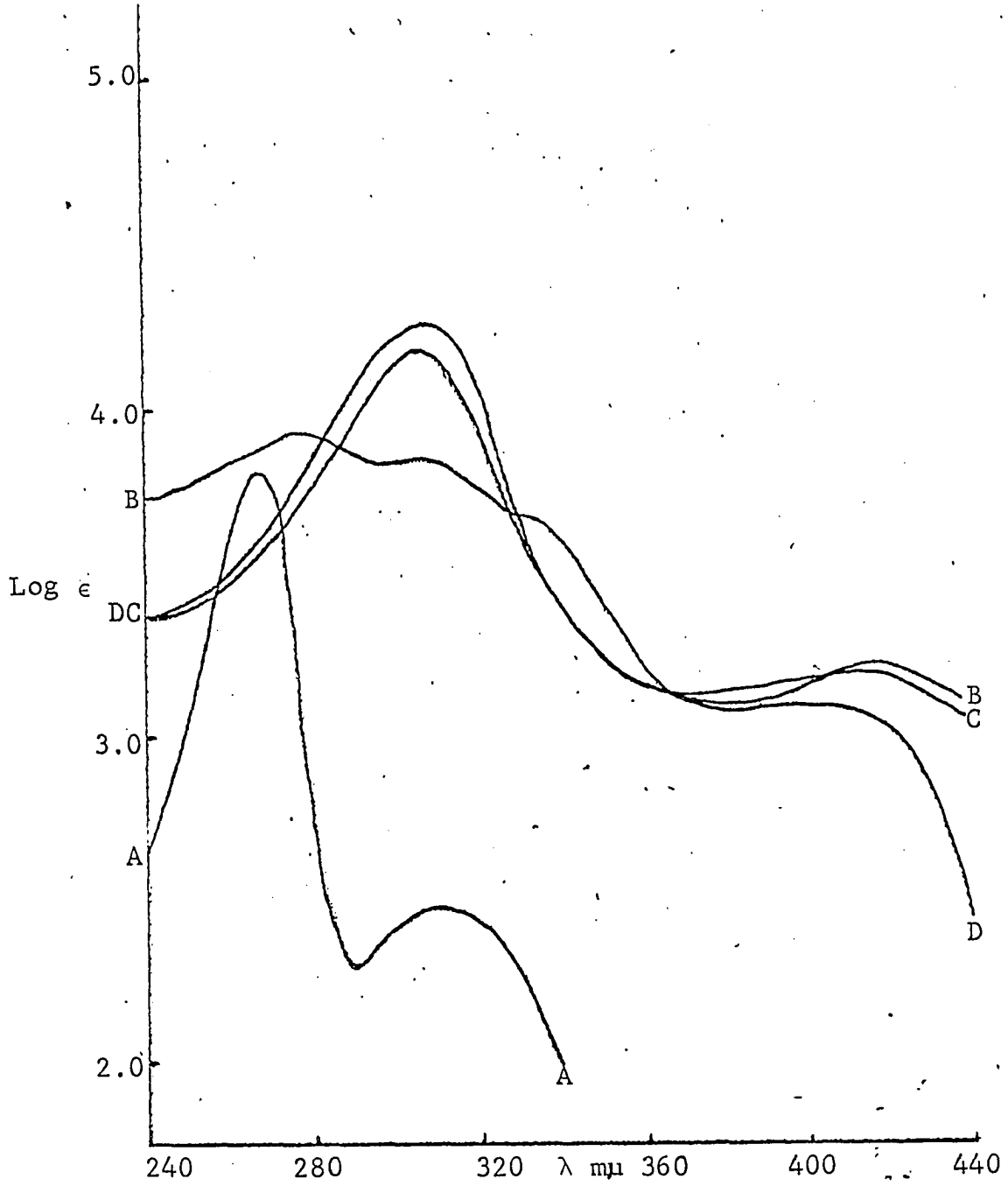
A = 1-Methyl-2,5-diphenylpyrazinium bromide in 95% Ethanol
B = First spectrum observed on addition of sodium borohydride
C = Second spectrum observed after addition of sodium borohydride
D = Spectrum observed after addition of acid
E = Final spectrum observed

Fig. 7



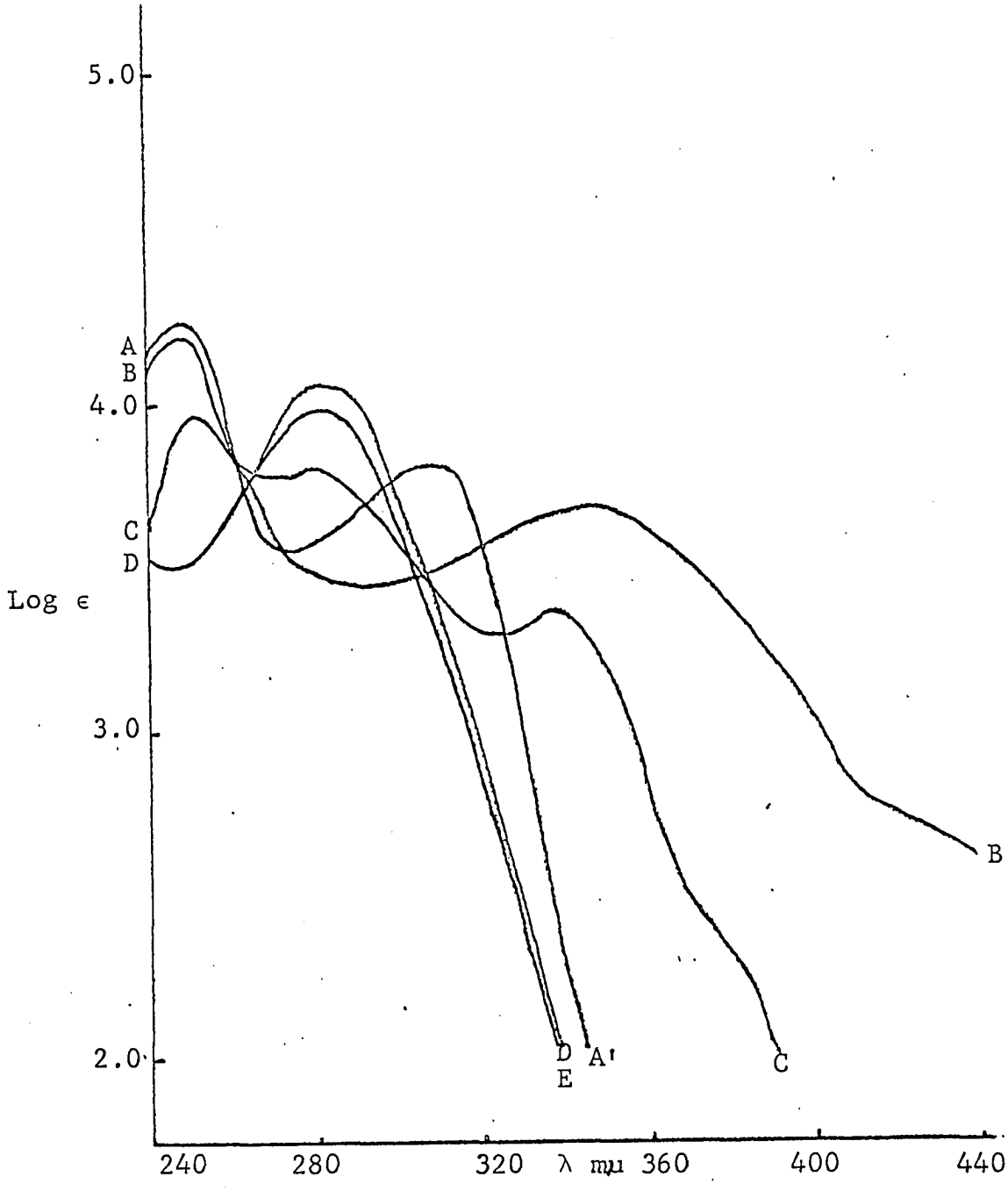
A = 1-Methyl-2,3-diphenylpyrazinium bromide in 95% Ethanol
B = First spectrum observed on addition of sodium borohydride
C = Second spectrum observed on addition of sodium borohydride
D = Spectrum observed after addition of acid and final spectrum observed

Fig. 8



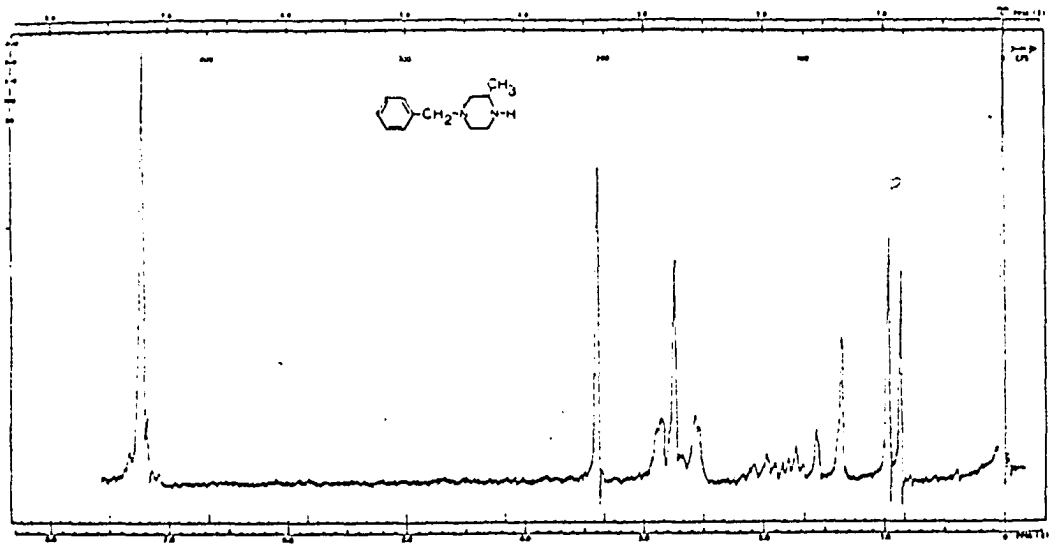
A = 1-Benzyl-3-carboxamidopyrazinium bromide in water
B = First spectrum observed on addition of sodium borohydride
C = Second spectrum observed on addition of sodium borohydride
D = Spectrum observed on addition of acid and final spectrum observed

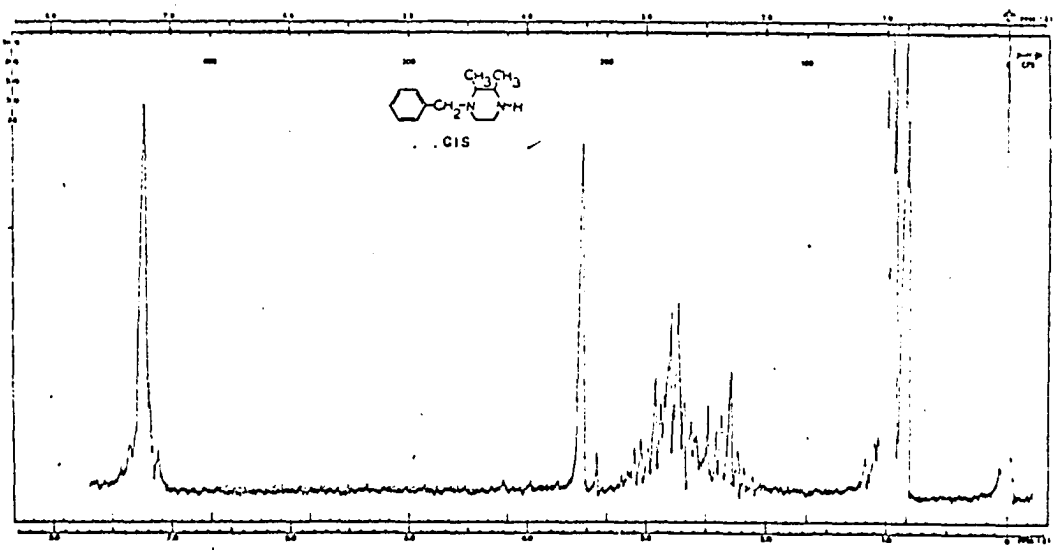
Fig. 9



A = 1-Methyl-3-cyanopyrazinium methanosulfate in water
B = First spectrum observed on addition of sodium borohydride
C = Second spectrum observed on addition of sodium borohydride
D = Spectrum observed on addition of acid
E = Final spectrum observed

NUCLEAR MAGNETIC RESONANCE SPECTRA





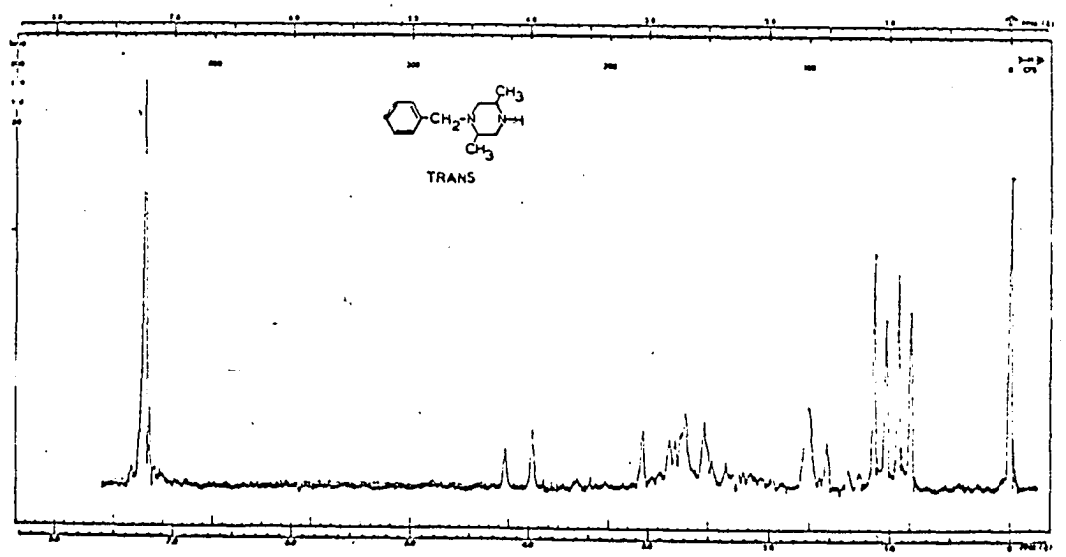
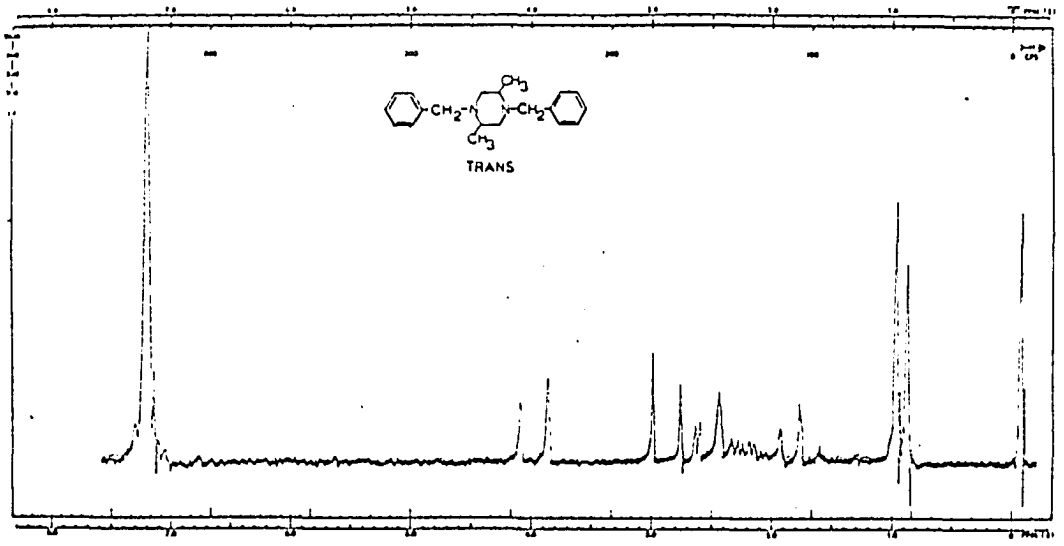
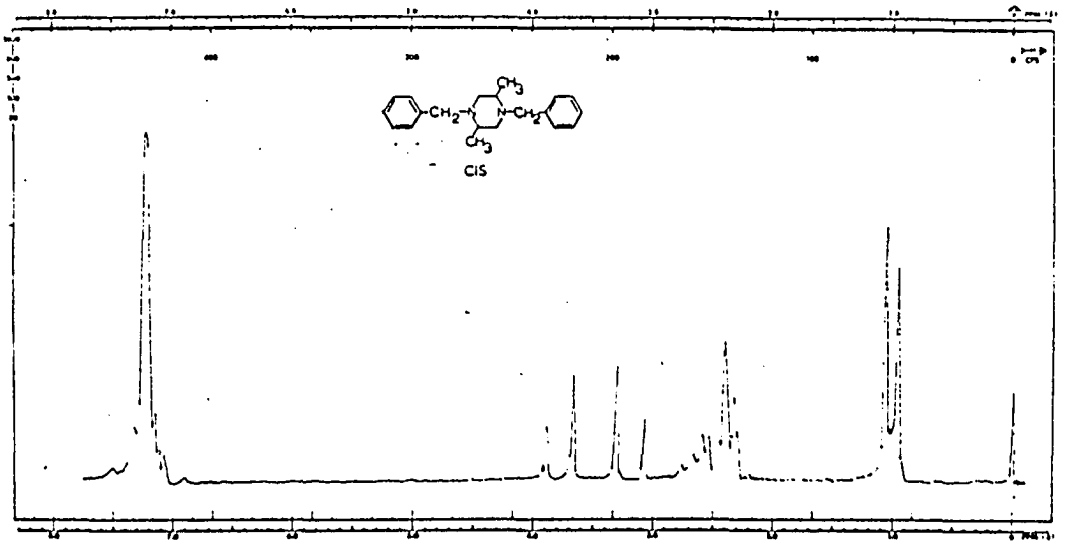


Fig. 10





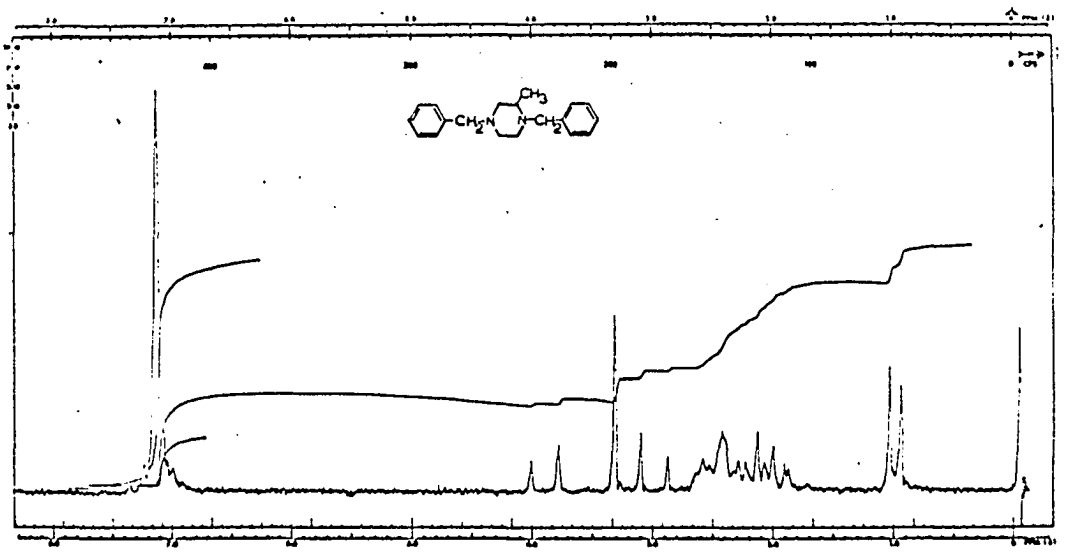
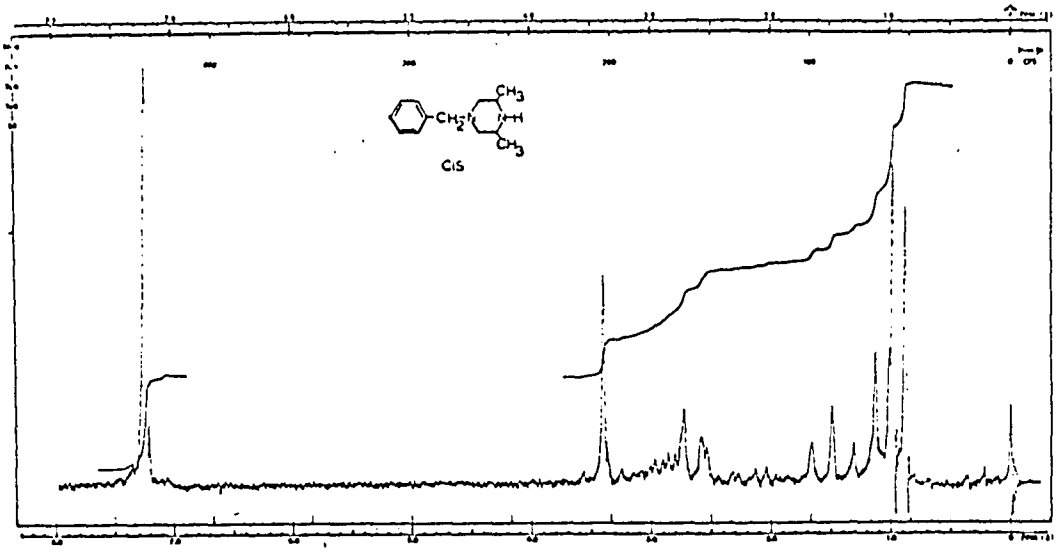


Fig. 11



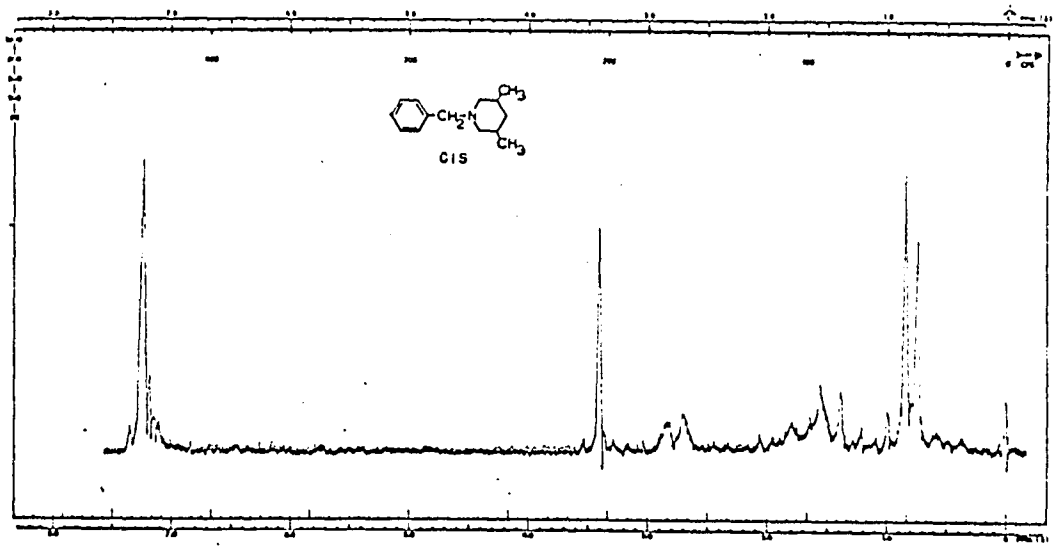
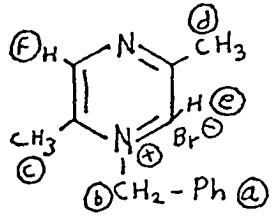
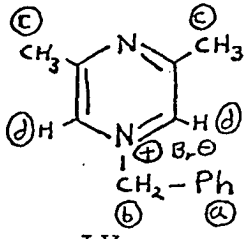
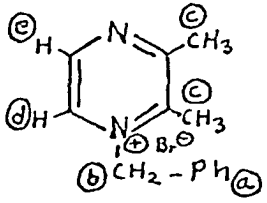
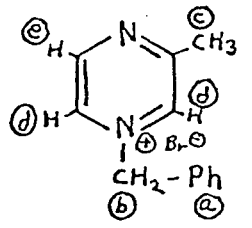
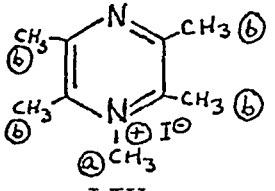
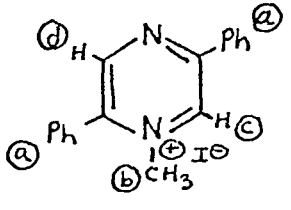
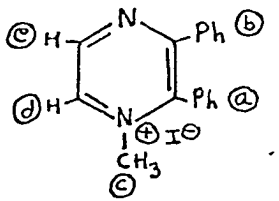
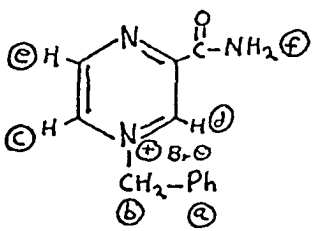
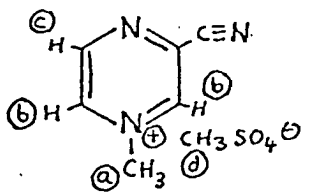


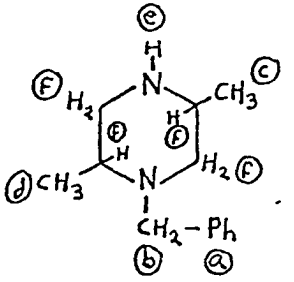
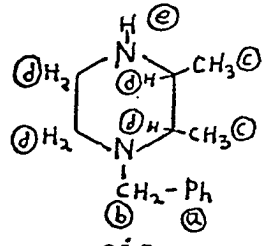
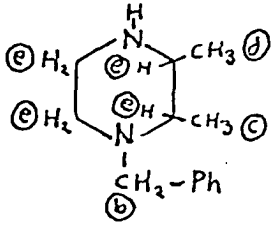
Fig. 12

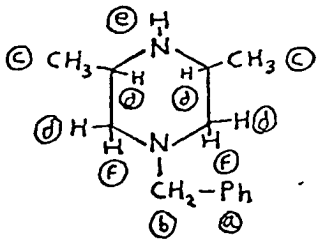
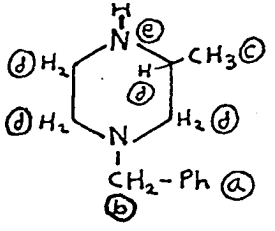
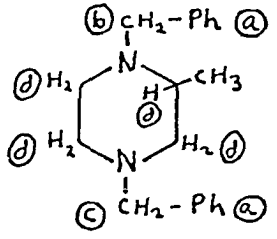
TABLE III

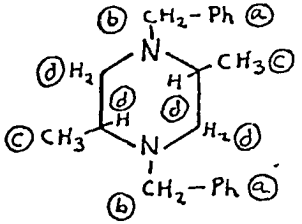
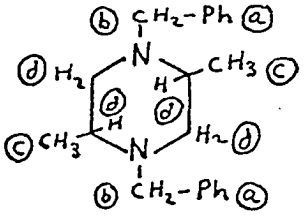
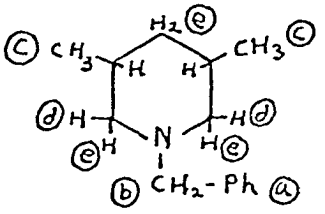
U.N.H. Spectrum No.	Compound	Chemical Shift p.p.m.	No. of Protons	Pattern	J.	Assignment	Solvent
418	 LVI	9.23	1	complex	-	f	D_2O
		8.73	1	complex	-	e	
		7.55	5	complex	-	a	
		5.95	2	singlet	-	b	
		2.90	3	singlet	-	c	
		2.80	3	singlet	-	d	
417	 LV	8.80	2	singlet	-	d	D_2O
		7.62	5	singlet	-	a	
		5.90	2	singlet	-	b	
		2.80	6	singlet	-	c	
816	 LVII	8.94	1	complex	-	e	D_2O
		8.57	1	doublet	4	d	
		7.35	5	complex	-	a	
		5.78	2	singlet	-	b	
		2.70	6	singlet	-	c	

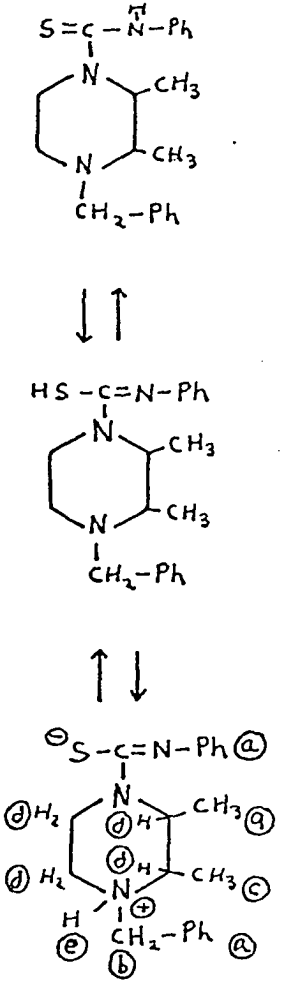
420	 LVIII	9.40	1	complex	-	e	D_2O
		9.02	2	complex	-	d	
		6.68	5	singlet	-	a	
		6.00	2	singlet	-	b	
		2.90	3	singlet	-	c	
951	 LIV	4.2	3	singlet	-	a	D_2O
		2.7	12	singlet	-	b	
914	 LIX	9.90	1	triplet	-	d	DMSO
		9.48	1	singlet	-	c	
		8.31	2	complex	-	a	
		7.78	8	complex	-	a	
		4.31	3	singlet	-	b	

915	 LX	9.62	1	complex	d	DMSO
		9.34	1	complex	e	
		7.58	5	singlet	a	
		7.32	5	singlet	b	
		4.12	3	singlet	c	
950	 LXI	9.59	1	complex	c	D_2O
		9.21	1	complex	d	
		8.80	1	complex	e	
		7.58	5	singlet	a	
		6.05	2	singlet	b	
		2.20	2	singlet	f	
1383a	 LXII	9.62	1	singlet	c	D_2O
		9.30	2	complex	b	
		4.60	3	singlet	a	
		3.68	3	singlet	d	

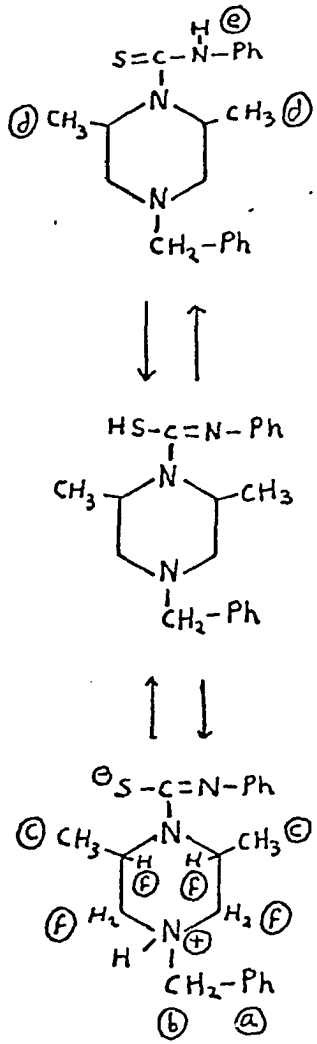
531	 trans LXV	7.23	5	singlet		a	CCl_4
		4.10	1	doublet	14	b	
		2.91	1	doublet	14	b	
		2.43	4	complex		f	
		1.57	2	doublet	8	f	
		1.32	1	singlet		e	
		1.07	3	doublet	5	d	
		0.87	3	doublet	5	c	
888a	 cis LXVI	7.30	5	singlet		a	CCl_4
		3.51	2	singlet		b	
		2.61	6	complex		d	
		1.00	1	singlet		e	
		0.81	3	doublet	5	c	
		0.82	3	doublet	5	c	
1450	 cis LXVI	3.48	2	singlet		b	Benzene
		2.53	6	complex		e	
		0.88	3	doublet	2	c	
		0.78	3	doublet	2	d	

492	 cis LXIV	7.24	5	singlet		a	CCl_4
		3.40	2	singlet		b	
		2.80	4	complex		d	
		2.49	2	triplet	11	f	
		1.14	1	singlet		e	
		0.93	6	doublet	6	c	
482	 LXIII	7.21	5	singlet		a	CCl_4
		3.40	2	singlet		b	
		2.75	5	complex		d	
		1.90	2	complex		d	
		1.36	1	singlet		e	
		0.90	3	doublet	5	c	
1375	 CXVI	7.08	10	singlet		a	CCl_4
		3.87	1	doublet	14	b	
		3.27	2	singlet		c	
		2.92	1	doublet	14	b	
		2.17	7	complex		d	
		0.95	3	doublet	5	e	

1134	 trans CXVII	7.27 4.04 2.94 2.33 0.97	10 2 2 6 6	singlet doublet doublet complex doublet	 14 14 5	a b b d c	CCl_4
1118	 cis CXVIII	7.20 3.78 3.20 2.53 1.00	10 2 2 6 6	singlet doublet doublet complex doublet	 14 14 5	a b b d c	CCl_4
1313	 LXIV	7.22 3.42 2.78 1.55 0.81	5 2 2 6 6	singlet singlet doublet complex doublet	 7 5	a b d e c	CCl_4

1016		7.62	1	complex		e
		7.20	10	complex		a
		4.88	1	complex		f
		4.08	1	doublet	14	b
		2.88	1	doublet	14	b
		2.50	6	complex		d
		1.26	3	doublet	7	c
		1.16	3	doublet	7	g

CXXVI

1034		7.25	10	two doublets		a	CCl_4
		4.70	1	complex		e	
		3.49	1	singlet		b	
		3.40	1	singlet		b	
		2.50	6	complex		b	
		1.33	3	doublet	7	d	
		0.91	3	doublet	7	c	

CXXIV

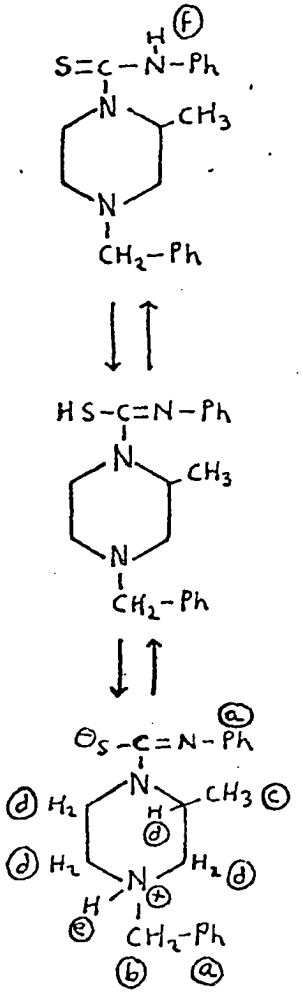
1035	 CXXIII	7.60	1	singlet		e	CCl_4
		7.18	10	complex		a	
		4.90	1	complex		f	
		4.10	1/2	doublet	14	b	
		3.43	1	singlet		b	
		3.08	1/2	doublet	14	b	
		2.40	7	complex		d	
		1.30	3	doublet	7	c	

TABLE IV

Ultraviolet Spectra

Compound (U.N.H. Spectrum No.)	Solvent	λ max	Log	λ max of intermediates upon addition of $NaBH_4$	Final λ max after addition of $NaBH_4$	Final λ max after addition of $NaBH_4$ and acid
LXII(370)	H_2O	248 310	4.24 3.83	350 283 430(s)*	283	no maxima
LXI(241)	H_2O	265 308	3.78 3.47	348(s) 306 414		
LXI(150)	2-Propanol	269 320(s)	3.87	266 342	266 342	280
LX(242)	CH_3OH	343 253	3.74 4.00	no maxima	no maxima	no maxima
LX(356)	95% Ethanol	342 256	3.79 4.05	356 300(s)	405	405
LIX(238)	75% of H_2O	272	4.26	300	no maxima	no maxima
	25% CH_3OH	352 392	3.94	354		

*s = shoulder

LIX(357)	95% Ethanol	352 271	4.31	296 388	296 388[1]	no maxima
LIX(239)	Methanol	271 351	3.93 3.68	305	no maxima	no maxima
LIV(239a)	H_2O	305	4.16	312	no maxima	no maxima
LIV(244)	95% Ethanol	300	4.05	no maxima	no maxima	no maxima
LVI(24)	H_2O	288	3.89	no maxima	no maxima	no maxima
LVI(144)	2-Propanol	288	3.92	320	no maxima	no maxima
LVI(49)	DMF	283	4.00	330	330	no maxima
LVII(243)	H_2O	278	3.83	no maxima	no maxima	no maxima
LVIII(145)	2-Propanol	278	3.82	336	no maxima	no maxima
LVIII(51)	DMF			320	no maxima	no maxima

1 = decreased

LV(21)	H_2O	285	3.83	no maxima	no maxima	no maxima
LV(18)	Methanol	286	3.85	no maxima	no maxima	no maxima
LV(40)	DMF			340	340	no maxima
LV(143)	2-Propanol	286	3.86	340	no maxima	no maxima
XLIV(151)	2-Propanol	268	4.18	268[1]	268[1]	268[1]
LVII(237)	H_2O	285	3.90	no maxima	no maxima	no maxima
XXXIX(178)	95% Ethanol	285 223 362	3.72 4.14 2.67			
L(146)	2-Propanol	271 276	3.81 3.82			
LI(146)	2-Propanol	270 274	3.82 3.83			
XLIX(146)	2-Propanol	265 271(s)	3.91			

TABLE V

Preparative Vapor Phase Chromatographic Data

No.	Source	Column Temp. °C	Collector Temp. °C	Injector Temp. °C	Detector Temp. °C	Flow Rate ml/min.	Retention Time mins. (% Rel. area)	Identity of Peak
1	Crude	210	190	200	225	400	35.5 (10)	LXIV
	LXV						58.5 (90)	
2	Crude LXIV from hydrogenation of salt	215	185	185	202	400	15.0 (19)	Unknown
							23.0 (81)	LXIV
3	Crude	180	200	210	210	400	11.6 (6.0)	LXII
	LXVI						48.2 (94)	LXVI

Column - 20% Carbowax 20M Chromosorb w- 60/80 mesh-acid washed - DMCS treated - 20' x 3/8"

TABLE V Cont.

No.	Source	Column Temp. °C	Collector Temp. °C	Injector Temp. °C	Detector Temp. °C	Flow Rate ml/min.	Retention Time mins. (% Rel. area)	Identity of Peak
4	Crude CXIV hydrogenation of $NaBH_4$ reduction product	205	185	220	200	400	23.2	CXIV
							53.0	Unknown
5	Product of cat. hydrogenation of LVI	215	195	210	225	400	69.0	Aldehyde

Table VI

Vapor Phase Chromatograph Data

No.	Source	Column	Temp°C	He Press. p.s.i.	Retention Time Mins. (% Rel. area)	Identity of Peak
1.	Prep. G.L.C. fraction 1 from prep. of LXV	a	175°	8	2.6 (95) 3.3 (5)	LXIV LXV
2.	Prep. G.L.C. fraction 2 from prep. of LXV	a	175°	8	2.6 (5) 3.4 (95)	LXIV LXV
3.	Prep. G.L.C. fraction 1 from separation of crude LXVI	a	175°	8	2.9 (84) 3.7 (s) (16)	LXIII LXVI

a = Carbowax 20 M, Chromosorb W, 1 M; b = Carbowax, 20 M Chromosorb W, 2M;
c = Silicone oil, 1M; d = Silicone nitrile, 1M; e = Carbowax 20 M, Haloport , 1M;
f = Carbowax 1500, 1M. (s) = Shoulder

Table VI Cont.

No.	Source	Column	Temp°C	He Press. p.s.i.	Retention Time Mins. (% Rel. area)	Identity of Peak
4.	Prep. G.L.C. fraction 2 from separation of crude LXVI	a	175°	8	2.8 (3)	LXIII
					3.9 (97)	LXVI
5.	Crude LXV	a	150°	8	5.2 (10)	LXIV
					7.1 (90)	LXV
6.	Crude LXV	a	150°	8	5.0 (45)	LXIV
	Pure LXIV				6.6 (55)	LXV
7.	Crude LXV	a	175°	8	2.4 (45)	LXIV
	Pure LXIV				3.2 (55)	LXV

Table VI Cont.

No.	Source	Column	Temp°C	He Press. p.s.i.	Retention Time Mins. (% Rel. area)	Identity of Peak
8.	Crude LXV	a	175°	8	2.5 (10)	LXIV
					3.3 (90)	LXV
9.	Crude LXV	c	175°	8	4.0 (10)	LXIV
					4.7 (90)	LXV
10.	Crude LXV	c	175°	8	4.1 (45)	LXIV
	Pure LXIV			8	4.8 (55)	LXV
11.	Crude LXV	d	128°	8	2.8 (s) (10)	LXIV
					3.5 (90)	LXV

Table VI Cont.

No.	Source	Column	Temp°C	He Press. p.s.i.	Retention Time Mins. (% Rel. area)	Identity of Peak
12.	Crude LXV	d	128°	8	2.5 (45)	LXIV
	Pure LXIV				3.5 (55)	LXV
13.	Crude LXV	a	125°	8	11.6 (10)	LXIV
					16.0 (90)	LXV
14.	Crude LXV	a	125	8	11.3 (40)	LXIV
	Pure LXIV				15.8 (60)	LXV
15.	Distilled LXVI	c	175°	8	3.2 (6)	LXIII
					5.0 (94)	LXVI

Table VI Cont.

No.	Source	Column	Temp°C	He Press. p.s.i.	Retention Time Mins. (% Rel. area)	Identity of Peak
16.	Distilled LXVI	d	150°	8	1.7 (11) 2.3 (89)	LXIII LXVI
17.	Distilled LXVI	a	150°	12	3.5 (6) 4.3 (94)	LXIII LXVI
18.	Distilled LXVI	a	150	8	4.9 (6) 6.3 (94)	LXIII LXVI
19.	Distilled LXIV	a	132	8	7.8 (100)	LXIV

Table VI Cont.

No.	Source	Column	Temp°C	He Press. p.s.i.	Retention Time Mins. (% Rel. area)	Identity of Peak
20.	Distilled LXIV	c	160	8	5.2 (100)	LXIV
21.	Distilled LXIV	f	150	8	1.5 (100)	LXIV
22.	LXV from picrate recrystallization	a	161	8	3.6 (0.5) 4.5 (99.5)	LXIV LXV
23.	LXV extract without treatment with acid or base	a	161	8	3.5 (13) 4.6 (87)	LXIV LXV
24.	LXIV without treatment with acid or base (soln.)	a	160	8	3.1 (100)	LXIV

Table VI Cont.

No.	Source	Column	Temp°C	He Press. p.s.i.	Retention Time Mins. (% Rel. area)	Identity of Peak
25	LXIII extract without treatment with acid or base	a	192	5	3.1 (100)	LXIII
26.	Distilled LXIII	e	200	4	2.0 (93)	LXIII
					5.4 (7)	Unknown
27.	Distilled LXIII	e	200	4	0.8 (2.0)	Unknown
					1.7 (98)	LXIII
28.	LXIV Distilled product from cat. hydrogenation	a	163	8	3.7 (90)	LXIV
					8.4 (10)	Unknown

Table VI Cont.

No.	Source	Column	Temp°C	He Press. p.s.i.	Retention Time Mins. (% Rel. area)	Identity of Peak
29	Distilled LXIII	e	167	12	1.4 (100)	LXIII
30.	Et_2O solv. of product of $NaBH_4$ reduction of LXI	a	192	8	4.1 (100)	Unknown
31.	Crude LI	a	150	8	0.20 (20) 0.22 (80)	Unknown LI
32.	Crude hydrogenation product of $NaBH_4$ reduction product of CXXI	a	150	8	2.2 (54) 2.8 (21) 7.7 (19) 15 (60)	CXIV Unknown Unknown

Table VI Cont.

No.	Source	Column	Temp°C	He Press. p.s.i.	Retention Time Mins. (% Rel. area)	Identity of Peak
33.	Product of $NaBH_4$ reduction of CXXI	a	150	8	2.2 (27)	CXIV
					3.3 (17)	Dihydro or tetra-hydro-pyridine
					3.8 (14)	1-Benzyl-3,5-di-methyl-piperidine
					7.5 (12)	Unknown
					14.0 (30)	Unknown
34.	Et_2O of product of $NaBH_4$ reduction of LX	a	190	12	4.2 (7.0)	Unknown
					6.9 (24)	Unknown
					11.0 (69)	Unknown

Table VI Cont.

No.	Source	Column	Temp°C	He Press. p.s.i.	Retention Time Mins. (% Rel. area)	Identity of Peak
35.	Product of cat. hydrogenation of CXXI	a	150	8	1.0 (17) 2.3 (83)	Unknown CXIV
36.	H_2O soln. of $NaBH_4$ reduction product of LIV	a	150	8	1.6 2.2 2.4 2.8 (74) 3.2 3.7 4.5 (26)	Unknown Unknown Unknown Unknown Unknown Unknown Unknown
37.	Et_2O extract of $NaBH_4$ reduction of LV in 1:4 molar ratio	a	174	5	2.2 2.6 4.8 (78) 5.4 5.86 (22)	Unknown Unknown Unknown Unknown LXIV

Table VI Cont.

No.	Source	Column	Temp°C	He Press. p.s.i.	Retention Time Mins. (% Rel. area)	Identity of Peak
38.	Commercial L	b	152	8	1.8 (90)	L
					2.6 (10)	Probably LI
39.	CXXIX	c	100	8	3.4	XCII
	XCIX				3.6	CXXIX
40.	CXXIX	b	126	8	2.3	CXXIX
	XCII				2.5	XCII
41.	Crude	b	175	10	8.2 (10)	LXIV
	LXV				11.0 (90)	LXV

Table VI Cont.

No.	Source	Column	Temp°C	He Press, p.s.i.	Retention Time Mins. (% Rel. area)	Identity of Peak
42.	Distilled LXIV	b	175	10	8.6 (100)	LXIV
43.	Crude LXVI	b	175	10	9.38 (50)	LXIII
					13.4 (95)	LXVI

SUMMARY

1. 1-Benzylmethylpyrazinium salts underwent reduction with sodium borohydride to give 1-benzylmethylpiperazines. Satisfactory yields were obtained with all compounds except with 1-benzyl-3-methylpyrazinium bromide.

2. The above reaction was proven to be stereospecific when more than one diasteroisomer could be formed.

3. Pyrazinium salts with phenyl, cyano, or carboxamido substituents gave tars on reduction with sodium borohydride.

4. The reduction of all the pyrazinium salts were followed in the ultraviolet spectrophotometer and the changes in ultraviolet absorption were found to be analogous to those observed in the pyridinium ion series.

5. The steric and electronic effects on the quaternization of piperazines were studied.

6. The nuclear magnetic resonance spectra of the series of 1-benzylmethylpiperazines showed that the magnetic equivalence or non-equivalence of the benzylic hydrogens were related to the stereochemistry of the methyl piperazine ring.

7. 1,4-Dibenzylmethylpiperazines were prepared and the nuclear magnetic resonance spectra were determined as a means to check the relationships of structure to magnetic equivalence and non-equivalence of the benzylic hydrogens. These results are discussed.

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